79 Rec'd PCT/PTO 30 JUL 1998

FORM PTO-1390 (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER IVD 913
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U. S. APPLICATION NO. (If known, see 37 CFR 1.5) 09/125005
INTERNATIONAL APPLICATION NO. PCT/FR97/00214	INTERNATIONAL FILING DATE February 3, 1997	PRIORITY DATE CLAIMED February 2, 1996
TITLE OF INVENTION	PURIFIED SR-p70 PROTEIN	
APPLICANT(S) FOR DO/EO/US CAPUT, Daniel, FERRARA, Pascual and KAGHAD, Ahmed Mourad		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND or SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1)).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371 (c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9 ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR 1 5)	INTERNATIONAL APPLICATION NO PCT/FR97/00214	ATTORNEY'S DOCKET NUMBER IVD 913

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1. 492 (a)(1)-(5)):

Search Report has been prepared by the EPO or JPO. $930.00
International preliminary examination fee paid to USPTO (37CFR 1.482) $720.00
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $790.00
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1,070.00
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4). $98.00

				CALCULATIONS	PTO USE ONLY
ENTER APPROPRIATE BASIC FEE AMOUNT =				$ 930.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	38-20 =	18	x $22.00	**$ 396.00**	
Independent claims	5 - 3 =	2	x $82.00	**$ 164.00**	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $270.00	$	
TOTAL OF ABOVE CALCULATIONS =				**$1490.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				**$1490.00**	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$	
TOTAL NATIONAL FEE =				$	
Fee for recording the enclosed assignment (37 CFR 1.21(h). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 40.00	
TOTAL FEES ENCLOSED =				**$1530.00**	
				Amount to be refunded:	$
				Charged	**$1530.00**

a. ☐ A check in the amount of $__________________ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 19-0091 in the amount of **$1530.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0091. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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Mary P. Bauman 7/29/98
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09/125005
Docket No. IVD 913

79 Rec'd PCT/PTO 30 JUL 1998

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Filing under 35 U.S.C. § 371
Corresponding to International Application Serial No.: PCT/FR97/00214

Applicants: CAPUT, Daniel, FERRARA, Bernard and KAGHAD, Mourad

International Filing Date: February 3, 1997

For: **PURIFIED SR-p70 PROTEIN**

CERTIFICATE UNDER 37 C.F.R. 1.10

Express Mail Label Number: EM317281100US

Date of Deposit: July 29, 1998

I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service on the date indicated above and is addressed to: Asst. Commissioner for Patents, Box PCT, Attn: EO/US, Washington, DC 20231.

Signature

Assistant Commissioner for Patents
Box PCT
Attn: EO/US
Washington, D.C. 20231

Dear Sir:

PRELIMINARY AMENDMENT

Please amend the above-identified application as follows:

In the Claims

Please amend Claims 1-36 and add Claims 37 and 38 as follows before calculating the filing fee for the above-identified application:

1.(Amended) A [Purified] purified polypeptide, comprising an amino acid sequence selected from the group consisting of:

a) [the] sequence SEQ ID No. 2;

b) [the] sequence SEQ ID No. 4;

c) [the] sequence SEQ ID No. 6;

d) [the] sequence SEQ ID No. 8;

e) [the] sequence SEQ ID No. 10;

f) [the] sequence SEQ ID No. 13;

g) [the] sequence SEQ ID No. 15;

h) [the] sequence SEQ ID No. 17;

i) [the] sequence SEQ ID No. 19; and

j) any biologically active sequence derived from SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19.

2. (Amended) A [Polypeptide] polypeptide according to Claim 1, [characterized in that it] [comprises] comprising [the] an amino acid sequence selected from the group consisting of SEQ ID No. 6, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and SEQ ID No. 19.

3. (Amended) A [Polypeptide] polypeptide according to Claim 1, [characterized in that it comprises] comprising [the] a sequence lying between:

- residue 110 and residue 310 of SEQ ID No. 2 or 6;
- residue 60 and residue 260 of SEQ ID No. 8.

4. (Amended) A [Polypeptide] polypeptide according to Claim 1, [characterized in that it] which [results] is produced from an alternative splicing of [the] messenger RNA of [the] a corresponding gene.

5. (Amended) A [Polypeptide] polypeptide according to [any one of the preceding claims,] Claim 1 [characterized in that it] that is a recombinant polypeptide produced in the form of a fusion protein.

6. (Amended) An [Isolated] isolated nucleic acid sequence coding for a polypeptide according to [any one of the preceding claims] Claim 1.

7. (Amended) An [Isolated] isolated nucleic acid sequence according to Claim 6, [characterized in that it is] said nucleic acid having a sequence selected from the group consisting of:

a) [the] sequence SEQ ID No. 1;

b) [the] sequence SEQ ID No. 3;

c) [the] sequence SEQ ID No. 5;

d) [the] sequence SEQ ID No. 7;

e) [the] sequence SEQ ID No. 9;

f) [the] sequence SEQ ID No. 11;

g) [the] sequence SEQ ID No. 12;

h) [the] sequence SEQ ID No. 14;

i) [the] sequence SEQ ID No. 16;

j) [the] sequence SEQ ID No. 18;

k)[the] nucleic acid sequences capable of hybridizing specifically with [the] sequence SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5, SEQ ID No. 7, SEQ ID No. 9, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 14, SEQ ID No. 16 or SEQ ID No. 18 or with [the] sequences complementary to them, or of hybridizing specifically with their proximal sequences; and

l) [the] sequences derived from the sequences a), b), c), d), e), f), g), h), i), j) or k) as a result of the degeneracy of the genetic code, mutation, deletion, insertion, and alternative splicing or an allelic variability.

8. (Amended) A [Nucleotide] nucleotide sequence according to Claim 6, [characterized in that it is a sequence] selected from the group consisting of SEQ ID No. 5, SEQ ID No. 12, SEQ ID No. 14, SEQ ID No. 16 and SEQ ID No. 18 and coding, respectively, for the polypeptide of sequences SEQ ID No. 6, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and SEQ ID No. 19.

9. (Amended) A [Cloning] cloning and/or expression vector containing a nucleic acid sequence according to [any one of Claims] Claim 6 [to 8].

10. (Amended) A [Vector] vector, according to Claim 9, [characterized in that it] which is [the] plasmid pSE1.

11. (Amended) A [Host] host cell transfected by a vector according to Claim 9 [or 10].

12. (Amended) A [Transfected] transfected host cell, according to Claim 11, [characterized in that it] which is *E. coli* MC 1061.

13. (Amended) A [Nucleotide] nucleotide probe or nucleotide primer[, characterized in that it] which hybridizes specifically with [any one of the sequences according to Claims] the nucleic acid of Claim 6 [to 8] or [the] a nucleic acid having sequences complementary to them or [the corresponding] messenger RNAs corresponding to them or [the corresponding] genes corresponding to them.

14. (Amended) A [Probe] probe or primer according to Claim 13[, characterized in] that [it] contains at least 16 nucleotides.

15. (Amended) A [Probe] probe or primer according to Claim 13 [characterized in that it] that comprises the whole of the sequence of the gene coding for [one of the polypeptides of Claim 1] a polypeptide, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of:

a) sequence SEQ ID No. 2;
b) sequence SEQ ID No. 4;
c) sequence SEQ ID No. 6;
d) sequence SEQ ID No. 8;
e) sequence SEQ ID No. 10;
f) sequence SEQ ID No. 13;
g) sequence SEQ ID No. 15;
h) sequence SEQ ID No. 17;
i) sequence SEQ ID No. 19; and
j) any biologically active sequence derived from SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19.

16.(Amended) A [Nucleotide] nucleotide probe or primer selected from the group consisting of the following oligonucleotides or sequences complementary to them:

SEQ ID No. 20: GCG AGC TGC CCT CGG AG
SEQ ID No. 21: GGT TCT GCA GGT GAC TCA G
SEQ ID No. 22: GCC ATG CCT GTC TAC AAG
SEQ ID No. 23: ACC AGC TGG TTG ACG GAG

SEQ ID No. 24: GTC AAC CAG CTG GTG GGC CAG
SEQ ID No. 25: GTG GAT CTC GGC CTC C
SEQ ID No. 26: AGG CCG GCG TGG GGA AG
SEQ ID No. 27: CTT GGC GAT CTG GCA GTA G
SEQ ID No. 28: GCG GCC ACG ACC GTG AC
SEQ ID No. 29: GGC AGC TTG GGT CTC TGG
SEQ ID No. 30: CTG TAC GTC GGT GAC CCC
SEQ ID No. 31: TCA GTG GAT CTC GGC CTC
SEQ ID No. 32: AGG GGA CGC AGC GAA ACC
SEQ ID No. 33: CCA TCA GCT CCA GGC TCT C
SEQ ID No. 34: CCA GGA CAG GCG CAG ATG
SEQ ID No. 35: GAT GAG GTG GCT GGC TGG A
SEQ ID No. 36: TGG TCA GGT TCT GCA GGT G
SEQ ID No. 37: CAC CTA CTC CAG GGA TGC
SEQ ID No. 38: AGG AAA ATA GAA GCG TCA GTC
SEQ ID No. 39: CAG GCC CAC TTG CCT GCC
and SEQ ID No. 40: CTG TCC CCA AGC TGA TGA G

17. (Amended) The [Use] use of a sequence according to [any one of Claims] Claim 6 [to 8,] for the manufacture of oligonucleotide primers for sequencing reactions or specific amplification reactions according to the PCR technique or any variant of the latter.

18. (Amended) A [Nucleotide] nucleotide primer pair[, characterized in that it comprises] comprising [the] primers selected from the group consisting of the following sequences:

a) sense primer: GCG AGC TGC CCT CGG AG (SEQ ID No. 20)
antisense primer: GGT TCT GCA GGT GAC TCA G (SEQ ID No. 21)

b) sense primer: GCC ATG CCT GTC TAC AAG (SEQ ID No. 22)
antisense primer: ACC AGC TGG TTG ACG GAG (SEQ ID No. 23)

c) sense primer: GTC AAC CAG CTG GTG GGC CAG (SEQ ID No. 24)
antisense primer: GTG GAT CTC GGC CTC C (SEQ ID No. 25)

d) sense primer: AGG CCG GCG TGG GGA AG (SEQ ID No. 26)

antisense primer: CTT GGC GAT CTG GCA GTA G (SEQ ID No. 27)

e) sense primer: GCG GCC ACG ACC GTG A (SEQ ID No. 28)
antisense primer: GGC AGC TTG GGT CTC TGG (SEQ ID No. 29)

f) sense primer: CTG TAC GTC GGT GAC CCC (SEQ ID No. 30)
antisense primer: TCA GTG GAT CTC GGC CTC (SEQ ID No. 31)

g) sense primer: AGG GGA CGC AGC GAA ACC (SEQ ID No. 32)
antisense primer: GGC AGC TTG GGT CTC TGG (SEQ ID No. 29)

h) sense primer: CCCCCCCCCCCCCCN (where N equals G, A or T)
antisense primer: CCA TCA GCT CCA GGC TCT C (SEQ ID No. 33)

i) sense primer: CCCCCCCCCCCCCCN (where N equals G, A or T)
antisense primer: CCA GGA CAG GCG CAG ATG (SEQ ID No. 34)

j) sense primer: CCCCCCCCCCCCCCCCN (where N equals G, A or T)
antisense primer: CTT GGC GAT CTG GCA GTA G (SEQ ID No. 27)

k) sense primer: CAC CTA CTC CAG GGA TGC (SEQ ID No. 37)
antisense primer: AGG AAA ATA GAA GCG TCA GTC (SEQ ID No. 38) and

l) sense primer: CAG GCC CAC TTG CCT GCC (SEQ ID No. 39)
antisense primer: CTG TCC CCA AGC TGA TGA G (SEQ ID No. 40)

19. (Amended) The [Use] use of a sequence according to [any one of Claims] Claim 6 [to 8,] [which is usable] in gene therapy.

20. (Amended) The [Use] use of a sequence according to [any one of Claims] Claim 6 [to 8,] for the production of diagnostic nucleotide probes or primers, or of antisense sequences which are usable in gene therapy.

21. (Amended) The [Use] use of nucleotide primers according to [any one of Claims] Claim 6 [to 8,] for sequencing.

22. (Amended) The [Use] use of a probe or primer according to [any one of Claims] Claim 13 [to 16,] as an *in vitro* diagnostic tool for the detection, by hybridization experiments, of nucleic acid sequences coding for a polypeptide, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of:

a) sequence SEQ ID No. 2;

b) sequence SEQ ID No. 4;

c) sequence SEQ ID No. 6;

d) sequence SEQ ID No. 8;

e) sequence SEQ ID No. 10;

f) sequence SEQ ID No. 13;

g) sequence SEQ ID No. 15;

h) sequence SEQ ID No. 17;

i) sequence SEQ ID No. 19; and

j) any biologically active sequence derived from SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19 [according to any one of Claims 1 to 4,] in biological samples, or for the demonstration of aberrant syntheses or of genetic abnormalities.

23.(Amended) A [Method] method of *in vitro* diagnosis for the detection of aberrant syntheses or of genetic abnormalities in the nucleic acid sequences coding for a polypeptide, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of:

a) sequence SEQ ID No. 2;

b) sequence SEQ ID No. 4;

c) sequence SEQ ID No. 6;

d) sequence SEQ ID No. 8;

e) sequence SEQ ID No. 10;

f) sequence SEQ ID No. 13;

g) sequence SEQ ID No. 15;

h) sequence SEQ ID No. 17;

i) sequence SEQ ID No. 19; and

j) any biologically active sequence derived from SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19

[according to any one of Claims 1 to 4, characterized in that it comprises] comprising the steps of:

- [the] bringing of a nucleotide probe according to [any one of Claims] Claim 13 [to 16] into contact with a biological sample under conditions permitting the formation of a hybridization complex between the [said] probe and the [abovementioned] nucleotide sequence, where appropriate after a prior step of amplification of the [abovementioned]nucleotide sequence;
- the detection of the hybridization complex [possibly] formed; and
- where appropriate, [the] sequencing of the hybridization complex' nucleotide sequence [forming the hybridization complex] with the probe of the invention.

24. (Amended) The [Use] use of a nucleic acid sequence according to [any one of Claims] Claim 6 [to 8,] for the production of a recombinant polypeptide wherein said polypeptide comprises an amino acid sequence selected from the group consisting of:

a) sequence SEQ ID No. 2;

b) sequence SEQ ID No. 4;

c) sequence SEQ ID No. 6;

d) sequence SEQ ID No. 8;

e) sequence SEQ ID No. 10;

f) sequence SEQ ID No. 13;

g) sequence SEQ ID No. 15;

h) sequence SEQ ID No. 17;

i) sequence SEQ ID No. 19; and

j) any biologically active sequence derived from SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19 [according to any one of Claims 1 to 5].

25. (Amended) A [Method] method of production of a recombinant SR-p70 protein, characterized in that transfected cells according to Claim [10 or] 11 are cultured under conditions permitting the expression of a recombinant polypeptide of sequence SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15,

SEQ ID No. 17 or SEQ ID No. 19 or any biologically active fragment or derivative, and in that the [said] recombinant polypeptide is recovered.

26. (Amended) Mono- or polyclonal antibodies or their fragments, chimeric antibodies or immunoconjugates, characterized in that they are capable of specifically recognizing a polypeptide according to [any one of Claims] Claim 1 [to 4].

27. (Amended) Use of the antibodies according to [the preceding claim,] Claim 26 for the purification or detection of a polypeptide , wherein said polypeptide comprises an amino acid sequence selected from the group consisting of:

a) sequence SEQ ID No. 2;
b) sequence SEQ ID No. 4;
c) sequence SEQ ID No. 6;
d) sequence SEQ ID No. 8;
e) sequence SEQ ID No. 10;
f) sequence SEQ ID No. 13;
g) sequence SEQ ID No. 15;
h) sequence SEQ ID No. 17;
i) sequence SEQ ID No. 19; and
j) any biologically active sequence derived from SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19 [according to any one of Claims 1 to 4] in a biological sample.

28. (Amended) A [Method] method of *in vitro* diagnosis of pathologies correlated with an expression or an abnormal accumulation of SR-p70 proteins, in particular the phenomena of carcinogenesis, from a biological sample, [characterized in that] comprising the steps of contacting at least one antibody according to Claim 25 [is brought into contact] with the said biological sample under conditions permitting the [possible] formation of specific immunological complexes between an SR-p70 protein and the said antibody or antibodies, and detecting the presence of [in that the] specific immunological complexes [possibly] formed [are detected].

29. (Amended) A [Kit] kit for the *in vitro* diagnosis of an expression or an abnormal accumulation of SR-p70 proteins in a biological sample and/or for measuring the level of expression of these proteins in the said sample, comprising:

- at least one antibody according to Claim 25, optionally bound to a support,
- means of visualization of the formation of specific antigen-antibody complexes between an SR-p70 protein and the said antibody, and/or means of quantification of these complexes.

30. (Amended) A [Method] method for the early diagnosis of tumour formation, [characterized in that] wherein autoantibodies directed against an SR-p70 protein are demonstrated in a serum sample drawn from an individual, according to the steps that [consist in] comprise bringing a serum sample drawn from an individual into contact with a polypeptide of the invention, optionally bound to a support, under conditions permitting the formation of specific immunological complexes between the said polypeptide and [the] autoantibodies [possibly] present in the serum sample, and in that the specific immunological complexes [possibly] formed are detected.

31. (Amended) A [Method] method of determination of an allelic variability, a mutation, a deletion, an insertion, a loss of heterozygosity or a genetic abnormality of the SR-p70 gene, characterized in that it utilizes at least one nucleotide sequence according to [any one of Claims] Claim 6 [to 8].

32. (Amended) A [Method] method of determination of an allelic variability of the SR-p70 gene at position -30 and -20 relative to the initiation ATG of exon 2 which may be involved in pathologies[, and characterized in that it comprises at least] comprising:

- a step during which exon 2 of the SR-p70 gene carrying the target sequence is amplified by PCR using a pair of oligonuclotide primers according to [any one of Claims] Claim 6 [to 8];
- a step during which the amplified products are treated with a restriction enzyme whose cleavage site corresponds to the allele sought and;

- a step during which at least one of the products of the enzyme reaction is detected or assayed.

33. (Amended) A [Pharmaceutical] pharmaceutical composition comprising an effective amount of [as active principle a] the polypeptide according to [any one of Claims] Claim 1 [to 4].

34. (Amended) A [Pharmaceutical] pharmaceutical composition according to [the preceding claim, characterized in that it comprises] Claim 33, comprising a polypeptide comprising an amino acid sequence selected from SEQ ID No. 6, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and SEQ ID No. 19.

35. (Amended) A [Pharmaceutical] pharmaceutical composition containing an inhibitor or an activator of SR-p70 activity.

36. (Amended) A [Pharmaceutical] pharmaceutical composition containing a polypeptide derived from a polypeptide according to [any one of Claims] Claim 1 [to 5, characterized in that it] which is an inhibitor or an activator of SR-p70.

Please add the following new claims.

37. (New) The use of a probe or primer according to Claim 16 as an *in vitro* diagnostic tool for the detection, by hybridization experiments, of nucleic acid sequences coding for a polypeptide, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of:

a) sequence SEQ ID No. 2;
b) sequence SEQ ID No. 4;
c) sequence SEQ ID No. 6;
d) sequence SEQ ID No. 8;
e) sequence SEQ ID No. 10;
f) sequence SEQ ID No. 13;
g) sequence SEQ ID No. 15;

h) sequence SEQ ID No. 17;

i) sequence SEQ ID No. 19; and

j) any biologically active sequence derived from SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19 in biological samples, or for the demonstration of aberrant syntheses or of genetic abnormalities.

38. (New) A method of *in vitro* diagnosis for the detection of aberrant syntheses or of genetic abnormalities in the nucleic acid sequences coding for a polypeptide, said polypetide comprising an amino acid sequence selected from the group consisting of:

a) sequence SEQ ID No. 2;

b) sequence SEQ ID No. 4;

c) sequence SEQ ID No. 6;

d) sequence SEQ ID No. 8;

e) sequence SEQ ID No. 10;

f) sequence SEQ ID No. 13;

g) sequence SEQ ID No. 15;

h) sequence SEQ ID No. 17;

i) sequence SEQ ID No. 19; and

j) any biologically active sequence derived from SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19

comprising the steps of:

- bringing of a nucleotide probe according to Claim 16 into contact with a biological sample under conditions permitting the formation of a hybridization complex between the probe and the nucleotide sequence, where appropriate, after a prior step of amplification of the nucleotide sequence;
- the detection of the hybridization complex formed; and
- where appropriate, sequencing of the hybridization complex' nucleotide sequence with the probe of the invention.

REMARKS

Claims 1-36 have been amended in order to limit the multiple dependencies of these claims and to present them in the appropriate U.S. claim format.

New claims 37 and 38 have been added by the foregoing amendments. Support for these amendments can be found, for example, in original claims 22 and 23, wherein the subject matter now claimed is specifically set forth.

Respectfully submitted,

Date: 29 July 1998

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ENGLISH TRANSLATION OF INTERNATIONAL PATENT APPLICATION PCT/FR97/00214

filed on February 3, 1997

in the name of SANOFI

SANOFI

PURIFIED SR-p70 PROTEIN

Abstract

The invention relates to new nucleic acid sequences of the family of tumour-suppressing genes related to the gene for the p53 protein, and to the corresponding protein sequences.

The invention relates to new nucleic acid sequences of the family of tumour-suppressing genes related to the gene for the p53 protein, and to the corresponding protein sequences.

The invention also relates to the prophylactic, therapeutic and diagnostic applications of these sequences, in particular in the field of pathologies linked to the phenomena of apoptosis or of cell transformation.

Tumour-suppressing genes perform a key role in protection against the phenomena of carcinogenesis, and any modification capable of bringing about the loss of one of these genes, its inactivation or its dysfunction may have oncogenic character, thereby creating favourable conditions for the development of a malignant tumour.

The authors of the present invention have identified transcription products of a new gene, as well as the corresponding proteins. This gene, SR-p70, is related to the p53 tumour-suppressing gene, the antitumour activity of which is linked to its transcription factor activity, and more specifically to the controls exerted on the activity of the Bax and Bcl-2 genes which are instrumental in the mechanisms of cell death.

Hence the present invention relates to purified SR-p70 proteins, or biologically active fragments of the latter.

The invention also relates to isolated nucleic acid sequences coding for the said proteins or their biologically active fragments, and to specific oligonucleotides obtained from these sequences.

It relates, in addition, to the cloning and/or expression vectors containing at least one of the nucleotide sequences defined above, and the host cells transfected by these cloning and/or expression vectors under conditions permitting the replication and/or expression of one of the said nucleotide sequences.

The methods of production of recombinant SR-p70 proteins or their biologically active fragments by the transfected host cells also form part of the invention.

The invention also comprises antibodies or antibody derivatives specific for the proteins defined above.

It relates, in addition, to methods of detection of cancers, either by measuring the accumulation of SR-p70 proteins in the tumours according to immunohistochemical techniques, or by demonstrating autoantibodies directed against these proteins in patients' serum.

The invention also relates to any inhibitor or activator of SR-p70 activity, for example of protein-protein interaction, involving SR-p70.

It also relates to antisense oligonucleotide sequences specific for the above nucleic acid sequences, capable of modulating *in vivo* the expression of the SR-p70 gene.

Lastly, the invention comprises a method of gene therapy, in which vectors such as, for example, inactivated viral vectors capable of transferring coding sequences for a protein according to the invention are injected into cells deficient for this protein, for purposes of regulating the phenomena of apoptosis or of reversion of transformation.

A subject of the present invention is a purified polypeptide comprising an amino acid sequence selected from:

a) the sequence SEQ ID No. 2;
b) the sequence SEQ ID No. 4;
c) the sequence SEQ ID No. 6;
d) the sequence SEQ ID No. 8;
e) the sequence SEQ ID No. 10;
f) the sequence SEQ ID No. 13;
g) the sequence SEQ ID No. 15;
h) the sequence SEQ ID No. 17;
i) the sequence SEQ ID No. 19;
j) any biologically active sequence derived from SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19.

In the description of the invention, the following definitions are used:

- SR-p70 protein: a polypeptide comprising an amino acid sequence selected from the sequences SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19, or any biologically active fragment or derivative of this polypeptide;

- derivative: any variant polypeptide of the polypeptide of sequence SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19, or any molecule resulting from a modification of a genetic and/or chemical nature of the sequence SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19, that is to say obtained by mutation, deletion, addition, substitution and/or chemical modification of a single amino acid or of a limited number of amino acids, as well as any isoform sequence, that is to say sequence identical to the sequence SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19, or to one of its fragments or modified sequences, containing one or more amino acids in the form of the D enantiomer, the said variant, modified or isoform sequences having retained at least one of the properties that make them biologically active;

- biologically active: capable of binding to DNA and/or of exerting transcription factor activity and/or of participating in the control of the cell cycle, of differentiation and of apoptosis and/or capable of being recognized by the antibodies specific for the polypeptide of sequence SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19, and/or capable of inducing antibodies which recognize this polypeptide.

The manufacture of derivatives may have different objectives, including especially that of increasing the

affinity of the polypeptide for DNA or its transcription factor activity, and that of improving its levels of production, of increasing its resistance to proteases, of modifying its biological activities or of endowing it with new pharmaceutical and/or biological properties.

Among the polypeptides of the invention, the polypeptide of human origin comprising the sequence SEQ ID No. 6, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No.17 or SEQ ID No. 19 is preferred. The polypeptide of 636 amino acids corresponding to the sequence SEQ ID No. 6 is more than 97% identical to the polypeptide of sequence SEQ ID No. 2.

The polypeptide of sequence SEQ ID No. 2 and that of sequence SEQ ID No. 4 are two expression products of the same gene, and the same applies to the sequences SEQ ID No. 8 and SEQ ID No. 10 and to the sequences SEQ ID No. 6, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19.

As will be explained in the examples, the polypeptide of sequence SEQ ID No. 4 corresponds to a premature termination of the peptide of sequence SEQ ID No. 2, linked to an alternative splicing of the longer transcript (messenger RNA), coding for the polypeptide of SEQ ID No. 2, of the corresponding gene. Similarly, in humans, the polypeptides corresponding to the sequences SEQ ID No. 6, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and SEQ ID No. 19, diverge in their composition in respect of the N- and/or C-terminal portions, this being the outcome of alternative splicing of the same primary transcript. The N-terminal peptide sequence of the sequence SEQ ID No. 10 is deleted, this being linked to an alternative splicing of its coding transcript.

Advantageously, the invention relates to a polypeptide corresponding to the DNA binding domain of one of the above polypeptides.

This domain corresponds to the sequence lying between residue 110 and residue 310 for the sequences SEQ ID No. 2 or 6, and between residue 60 and residue 260 for the sequence SEQ ID No. 8.

A subject of the present invention is also nucleic acid sequences coding for a SR-p70 protein or biologically active fragments or derivatives of the latter.

More preferably, a subject of the invention is an isolated nucleic acid sequence selected from:

a) the sequence SEQ ID No. 1;

b) the sequence SEQ ID No. 3;

c) the sequence SEQ ID No. 5;

d) the sequence SEQ ID No. 7;

e) the sequence SEQ ID No. 9;

f) the sequence SEQ ID No. 11;

g) the sequence SEQ ID No. 12;

h) the sequence SEQ ID No. 14;

i) the sequence SEQ ID No. 16;

j) the sequence SEQ ID No. 18;

k) the nucleic acid sequences capable of hybridizing specifically with the sequence SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5, SEQ ID No. 7, SEQ ID No. 9, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 14, SEQ ID No. 16 or SEQ ID No. 18 or with the sequences complementary to them, or of hybridizing specifically with their proximal sequences;

l) the sequences derived from the sequences a), b), c), d), e), f), g), h), i), j) or k) as a result of the degeneracy of the genetic code.

According to a preferred embodiment, a subject of the invention is nucleotide sequences SEQ ID No. 5, SEQ ID No. 12, SEQ ID No. 14, SEQ ID No. 16 and SEQ ID No. 18, corresponding, respectively, to the cDNAs of the human proteins of the sequences SEQ ID No. 6, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and SEQ ID No. 19.

The different nucleotide sequences of the invention may be of artificial origin or otherwise. They can be DNA or RNA sequences obtained by the screening of libraries of sequences by means of probes prepared on the basis of the sequences SEQ ID No. 1, 3, 5, 7, 9, 11, 12, 14, 16 or 18. Such libraries may be prepared by traditional techniques of molecular biology which are

known to a person skilled in the art.

The nucleotide sequences according to the invention may also be prepared by chemical synthesis, or alternatively by mixed methods including the chemical or enzymatic modification of sequences obtained by the screening of libraries.

These nucleotide sequences enable nucleotide probes to be produced which are capable of hybridizing strongly and specifically with a nucleic acid sequence, of a genomic DNA or of a messenger RNA, coding for a polypeptide according to the invention or a biologically active fragment of the latter. Such probes also form part of the invention. They may be used as an *in vitro* diagnostic tool for the detection, by hybridization experiments, of transcripts specific for the polypeptides of the invention in biological samples, or for the demonstration of aberrant syntheses or of genetic abnormalities such as loss of heterozygosity or genetic rearrangement resulting from a polymorphism, from mutations or from a different splicing.

The probes of the invention contain at least 10 nucleotides, and contain at most the whole of the sequence of the SR-p70 gene or of its cDNA contained, for example, in a cosmid.

Among the shortest probes, that is to say of approximately 10 to 20 nucleotides, the appropriate hybridization conditions correspond to the stringent conditions normally used by a person skilled in the art.

The temperature used is preferably between T_m -5°C and T_m -30°C, and as a further preference between T_m -5°C and T_m -10°C, T_m being the melting temperature, the temperature at which 50% of the paired DNA strands separate.

The hybridization is preferably conducted in solutions of high ionic strength, such as, in particular, 6 x SSC solutions.

Advantageously, the hybridization conditions used are as follows:

- temperature: 42°C,

- hybridization buffer: 6 × SSC, 5 × Denhart's, 0.1% SDS, as described in Example III.

Advantageously, these probes are represented by the following oligonucleotides or the sequences complementary to them:

SEQ ID No. 20: GCG AGC TGC CCT CGG AG
SEQ ID No. 21: GGT TCT GCA GGT GAC TCA G
SEQ ID No. 22: GCC ATG CCT GTC TAC AAG
SEQ ID No. 23: ACC AGC TGG TTG ACG GAG
SEQ ID No. 24: GTC AAC CAG CTG GTG GGC CAG
SEQ ID No. 25: GTG GAT CTC GGC CTC C
SEQ ID No. 26: AGG CCG GCG TGG GGA AG
SEQ ID No. 27: CTT GGC GAT CTG GCA GTA G
SEQ ID No. 28: GCG GCC ACG ACC GTG AC
SEQ ID No. 29: GGC AGC TTG GGT CTC TGG
SEQ ID No. 30: CTG TAC GTC GGT GAC CCC
SEQ ID No. 31: TCA GTG GAT CTC GGC CTC
SEQ ID No. 32: AGG GGA CGC AGC GAA ACC
SEQ ID No. 33: CCA TCA GCT CCA GGC TCT C
SEQ ID No. 34: CCA GGA CAG GCG CAG ATG
SEQ ID No. 35: GAT GAG GTG GCT GGC TGG A
SEQ ID No. 36: TGG TCA GGT TCT GCA GGT G
SEQ ID No. 37: CAC CTA CTC CAG GGA TGC
SEQ ID No. 38: AGG AAA ATA GAA GCG TCA GTC
SEQ ID No. 39: CAG GCC CAC TTG CCT GCC
SEQ ID No. 40: CTG TCC CCA AGC TGA TGA G

Preferably, the probes of the invention are labelled prior to their use. To this end, several techniques are within the capacity of a person skilled in the art (fluorescent, radioactive, chemoluminescence, enzyme, and the like, labelling).

The *in vitro* diagnostic methods in which these nucleotide probes are employed are included in the subject of the present invention.

These methods relate, for example, to the detection of abnormal syntheses (e.g. accumulation of transcription products) or of genetic abnormalities, such as loss of heterozygosity and genetic rearrangement, and point mutations in the nucleotide sequences of nucleic

acids coding for an SR-p70 protein, according to the definition given above.

The nucleotide sequences of the invention are also useful for the manufacture and use of oligonucleotide primers for sequencing reactions or specific amplification reactions according to the so-called PCR technique or any variant of the latter (ligase chain reaction (LCR), etc).

Preferred primer pairs consist of primers selected from the nucleotide sequences: SEQ ID No. 1: monkey sequence of 2,874 nucleotides, and SEQ ID No. 5: human SR-p70a cDNA, in particular upstream of the ATG translation initiation codon and downstream of the TGA translation stop codon.

Advantageously, these primers are represented by the following pairs:

- pair No. 1:
sense primer: GCG AGC TGC CCT CGG AG (SEQ ID No. 20)
antisense primer: GGT TCT GCA GGT GAC TCA G (SEQ ID No. 21)

- pair No. 2:
sense primer: GCC ATG CCT GTC TAC AAG (SEQ ID No. 22)
antisense primer: ACC AGC TGG TTG ACG GAG (SEQ ID No. 23)

- pair No. 3:
sense primer: GTC AAC CAG CTG GTG GGC CAG (SEQ ID No. 24)
antisense primer: GTG GAT CTC GGC CTC C (SEQ ID No. 25)

- pair No. 4:
sense primer: AGG CCG GCG TGG GGA AG (SEQ ID No. 26)
antisense primer: CTT GGC GAT CTG GCA GTA G (SEQ ID No. 27)

- pair No. 5:
sense primer: GCG GCC ACG ACC GTG A (SEQ ID No. 28)
antisense primer: GGC AGC TTG GGT CTC TGG (SEQ ID No. 29)

- pair No. 6:
sense primer: CTG TAC GTC GGT GAC CCC (SEQ ID No. 30)
antisense primer: TCA GTG GAT CTC GGC CTC (SEQ ID No. 31)

- pair No. 7:
sense primer: AGG GGA CGC AGC GAA ACC (SEQ ID No. 32)
antisense primer: GGC AGC TTG GGT CTC TGG (SEQ ID No. 29)

- <u>pair No. 8</u>:
sense primer: CCCCCCCCCCCCCCN (where N equals G, A or T)
antisense primer: CCA TCA GCT CCA GGC TCT C (SEQ ID No. 33)

- <u>pair No. 9</u>:
sense primer: CCCCCCCCCCCCCCN (where N equals G, A or T)
antisense primer: CCA GGA CAG GCG CAG ATG (SEQ ID No. 34)

- <u>pair No. 10</u>:
sense primer: CCCCCCCCCCCCCCCN (where N equals G, A or T)
antisense primer: CTT GGC GAT CTG GCA GTA G (SEQ ID No. 27)

- <u>pair No. 11</u>:
sense primer: CAC CTA CTC CAG GGA TGC (SEQ ID No. 37)
antisense primer: AGG AAA ATA GAA GCG TCA GTC (SEQ ID No. 38)

- <u>pair No. 12</u>:
sense primer: CAG GCC CAC TTG CCT GCC (SEQ ID No. 39)
antisense primer: CTG TCC CCA AGC TGA TGA G (SEQ ID No. 40)

These primers correspond to the sequences extending, respectively:

- from nucleotide No. 124 to nucleotide No. 140 on SEQ ID No. 1 and from nucleotide No. 1 to nucleotide No. 17 on SEQ ID No. 5 for SEQ ID No. 20
- from nucleotide No. 2280 to nucleotide No. 2262 on SEQ ID No. 1 and from nucleotide No. 2156 to nucleotide 2138 on SEQ ID No. 5 for SEQ ID No. 21
- from nucleotide No. 684 to nucleotide No. 701 on SEQ ID No. 1 for SEQ ID No. 22
- from nucleotide No. 1447 to nucleotide No. 1430 on SEQ ID No. 1 and from nucleotide 1324 to nucleotide 1307 on SEQ ID No. 5 for SEQ ID No. 23
- from nucleotide 1434 to nucleotide 1454 on SEQ ID No. 1 and from nucleotide 1311 to nucleotide 1331 on SEQ ID No. 5 for SEQ ID No. 24
- from nucleotide 2066 to nucleotide 2051 on SEQ ID No. 1 and from nucleotide 1940 to nucleotide

1925 on SEQ ID No. 5 for SEQ ID No. 25

- from nucleotide 16 to nucleotide 32 on SEQ ID No. 5 for SEQ ID No. 26
- from nucleotide 503 to nucleotide 485 on SEQ ID No. 5 for SEQ ID No. 27
- from nucleotide 160 to nucleotide 176 on SEQ ID No. 11 for SEQ ID No. 28
- from nucleotide 1993 to nucleotide 1976 on SEQ ID No. 5 for SEQ ID No. 29
- from nucleotide 263 to nucleotide 280 on SEQ ID No. 11 for SEQ ID No. 30
- from nucleotide 1943 to nucleotide 1926 on SEQ ID No. 5 for SEQ ID No. 31
- from nucleotide 128 to nucleotide 145 on the nucleotide sequence depicted in Figure 22 for SEQ ID No. 32
- from nucleotide 1167 to nucleotide 1149 on SEQ ID No. 5 for SEQ ID No. 33
- from nucleotide 928 to nucleotide 911 on SEQ ID No. 5 for SEQ ID No. 34
- from nucleotide 677 to nucleotide 659 on SEQ ID No. 5 for SEQ ID No. 35
- from nucleotide 1605 to nucleotide 1587 on SEQ ID No. 5 for SEQ ID No. 36
- from nucleotide 1 to nucleotide 18 on the nucleotide sequence depicted in Figure 13 for SEQ ID No. 37
- from nucleotide 833 to nucleotide 813 on the nucleotide sequence depicted in Figure 13 for SEQ ID No. 38
- from nucleotide 25 to nucleotide 42 on the nucleotide sequence depicted in Figure 13 for SEQ ID No. 39
- from nucleotide 506 to nucleotide 488 on the nucleotide sequence depicted in Figure 13 for SEQ ID No. 40

The nucleotide sequences according to the invention can have, moreover, uses in gene therapy, in particular for controlling the phenomena of apoptosis and

of reversion of transformation.

The nucleotide sequences according to the invention may, moreover, be used for the production of recombinant SR-p70 proteins, according to the definition which has been given to this term.

These proteins may be produced from the nucleotide sequences defined above, according to techniques of production of recombinant products which are known to a person skilled in the art. In this case, the nucleotide sequence used is placed under the control of signals permitting its expression in a cell host.

An effective system for production of a recombinant protein necessitates having at one's disposal a vector, for example of plasmid or viral origin, and a compatible host cell.

The cell host may be selected from prokaryotic systems such as bacteria, or eukaryotic systems such as, for example, yeasts, insect cells, CHO cells (Chinese hamster ovary cells) or any other system advantageously available. A preferred cell host for the expression of proteins of the invention consists of the *E. coli* bacterium, in particular the strain MC 1061 (Clontec).

The vector must contain a promoter, translation initiation and termination signals and also the appropriate transcription regulation regions. It must be capable of being maintained stably in the cell and can, where appropriate, possess particular signals specifying the secretion of the translated protein.

These various control signals are selected in accordance with the cell host used. To this end, the nucleotide sequences according to the invention may be inserted into vectors which are autonomously replicating within the selected host, or vectors which are integrative for the chosen host. Such vectors will be prepared according to methods commonly used by a person skilled in the art, and the clones resulting therefrom may be introduced into a suitable host by standard methods such as, for example, electroporation.

The cloning and/or expression vectors containing

at least one of the nucleotide sequences defined above also form part of the present invention.

A preferred cloning and expression vector is the plasmid pSE1, which contains the elements necessary for its use both as a cloning vector in *E. coli* (origin of replication in *E. coli* and ampicillin resistance gene originating from the plasmid pTZ 18R) and as an expression vector in animal cells (promoter, intron, polyadenylation site, origin of replication of the SV40 virus), as well as the elements enabling it to be copied as a single strand with the object of sequencing (origin of replication of phage f1).

The characteristics of this plasmid are described in Application EP 0,506,574.

Its construction and also the integration of the cDNAs originating from the nucleic acid sequences of the invention are, moreover, described in the examples below.

According to a preferred embodiment, the proteins of the invention are in the form of fusion proteins, in particular in the form of a protein fused with glutathione S-transferase (GST). A designated expression vector in this case is represented by the plasmid vector pGEX-4T-3 (Pharmacia ref-27.4583).

The invention relates, in addition, to the host cells transfected by these aforementioned vectors. These cells may be obtained by introducing into host cells a nucleotide sequence inserted into a vector as defined above, followed by culturing of the said cells under conditions permitting the replication and/or expression of the transfected nucleotide sequence.

These cells are usable in a method of production of a recombinant polypeptide of sequence SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 12, SEQ ID No. 14, SEQ ID No. 16 or SEQ ID No. 18 or any biologically active fragment or derivative of the latter.

The method of production of a polypeptide of the invention in recombinant form is itself included in the present invention, and is characterized in that the

transfected cells are cultured under conditions permitting the expression of a recombinant polypeptide of sequence SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 12, SEQ ID No. 14, SEQ ID No. 16 or SEQ ID No. 18 or of any biologically active fragment or derivative of the latter, and in that the said recombinant polypeptide is recovered.

The purification methods used are known to a person skilled in the art. The recombinant polypeptide may be purified from lysates and cell extracts or from the culture medium supernatant, by methods used individually or in combination, such as fractionation, chromatographic methods, immunoaffinity techniques using specific mono- or polyclonal antibodies, and the like. A preferred variant consists in producing a recombinant polypeptide fused to a "carrier" protein (chimeric protein). The advantage of this system is that it permits a stabilization and a decrease in proteolysis of the recombinant product, an increase in solubility during *in vitro* renaturation and/or a simplification of the purification when the fusion partner possesses an affinity for a specific ligand.

Advantageously, the polypeptides of the invention are fused with glutathione S-transferase at the N-terminal position (Pharmacia "GST" system). The fusion product is, in this case, detected and quantified by means of the enzyme activity of the GST. The colorimetric reagent used is a glutathione acceptor, a substrate for GST. The recombinant product is purified on a chromatographic support to which glutathione molecules have been coupled beforehand.

The mono- or polyclonal antibodies capable of specifically recognizing an SR-p70 protein according to the definition given above also form part of the invention. Polyclonal antibodies may be obtained from the serum of an animal immunized against protein, produced, for example, by genetic recombination according to the method described above, according to standard procedures.

The monoclonal antibodies may be obtained

according to the traditional hybridoma culture method described by Köhler and Milstein, Nature, 1975, *256*, 495-497.

Advantageous antibodies are antibodies directed against the central region lying between residue 110 and residue 310 for the sequences SEQ ID No. 2 or 6, or between residue 60 and residue 260 for the sequence SEQ ID No. 8.

The antibodies according to the invention are, for example, chimeric antibodies, humanized antibodies or Fab and $F(ab')_2$ fragments. They may also take the form of immunoconjugates or labelled antibodies.

Moreover, besides their use for the purification of the recombinant polypeptides, the antibodies of the invention, especially the monoclonal antibodies, may also be used for detecting these polypeptides in a biological sample.

Thus they constitute a means of immunocytochemical or immunohistochemical analysis of the expression of SR-p70 proteins on sections of specific tissues, for example by immunofluorescence, gold labelling or enzyme immunoconjugates.

They make it possible, in particular, to demonstrate an abnormal accumulation of SR-p70 proteins in certain tissues or biological samples, which makes them useful for detecting cancers or monitoring the progression or remission of pre-existing cancers.

More generally, the antibodies of the invention may be advantageously employed in any situation where the expression of an SR-p70 protein has to be observed.

Hence the invention also relates to a method of *in vitro* diagnosis of pathologies correlated with an expression or an abnormal accumulation of SR-p70 proteins, in particular the phenomena of carcinogenesis, from a biological sample, characterized in that at least one antibody of the invention is brought into contact with the said biological sample under conditions permitting the possible formation of specific immunological complexes between an SR-p70 protein and the said

antibody or antibodies, and in that the specific immunological complexes possibly formed are detected.

The invention also relates to a kit for the *in vitro* diagnosis of an abnormal expression or accumulation of SR-p70 proteins in a biological sample and/or for measuring the level of expression of this protein in the said sample, comprising:

- at least one antibody specific for an SR-p70 protein, optionally bound to a support,
- means of visualization of the formation of specific antigen-antibody complexes between an SR-p70 protein and the said antibody, and/or means of quantification of these complexes.

The invention also relates to a method of early diagnosis of tumour formation, by detecting autoantibodies directed against an SR-p70 protein in an individual's serum.

Such a method of early diagnosis is characterized in that a serum sample drawn from an individual is brought into contact with a polypeptide of the invention, optionally bound to a support, under conditions permitting the formation of specific immunological complexes between the said polypeptide and the autoantibodies possibly present in the serum sample, and in that the specific immunological complexes possibly formed are detected.

A subject of the invention is also a method of determination of an allelic variability, a mutation, a deletion, an insertion, a loss of heterozygosity or a genetic abnormality of the SR-p70 gene which may be involved in pathologies, characterized in that it utilizes at least one nucleotide sequence described above. Among the methods of determination of an allelic variability, a mutation, a deletion, an insertion, a loss of heterozygosity or a genetic abnormality of the SR-p70 gene, preference is given to the method which is characterized in that it comprises at least one step of PCR amplification of the target nucleic acid sequence of SR-p70 liable to exhibit a polymorphism, a mutation, a

deletion or an insertion, using a pair of primers of nucleotide sequences defined above, a step during which the amplified products are treated using a suitable restriction enzyme and a step during which at least one of the products of the enzyme reaction is detected or assayed.

The invention also comprises pharmaceutical compositions comprising as active principle a polypeptide corresponding to the above definitions, preferably in soluble form, in combination with a pharmaceutically acceptable vehicle.

Such compositions afford a novel approach to treating the phenomena of carcinogenesis at the level of the control of multiplication and cell differentiation.

Preferably, these compositions can be administered systemically, preferably intravenously, intramuscularly, intradermally or orally.

Their optimal modes of administration, dosages and pharmaceutical dosage forms may be determined according to the criteria generally borne in mind in establishing a therapeutic treatment suitable for a patient, such as, for example, the patient's age or body weight, the severity of his or her general state, the tolerability of treatment and the observed side effects, and the like.

Lastly, the invention comprises a method of gene therapy, in which nucleotide sequences coding for an SR-p70 protein are transferred to target cells by means of inactivated viral vectors.

Other features and advantages of the invention are to be found in the remainder of the description, with the examples and the figures for which the legends are given below.

LEGEND TO THE FIGURES

Figure 1: Nucleic acid comparison of monkey SR-p70a cDNA (corresponding to SEQ ID No. 1) with the nucleic acid sequence of monkey p53 cDNA.

Figure 2: Protein comparison of monkey SR-p70a with monkey p53 protein (sw: p53-cerae).

Figure 3: Comparison of the nucleic acid sequence of monkey SR-p70a and b cDNA (corresponding, respectively, to SEQ ID No. 1 and SEQ ID No. 3).

Figure 4: Nucleic acid sequence and deduced protein sequence of monkey SR-p70a.

Figure 5: Partial nucleic acid sequence and complete deduced protein sequence of monkey SR-p70b.

Figure 6: Partial nucleic acid sequence and deduced complete protein sequence of human SR-p70a (corresponding to SEQ ID No. 5).

Figure 7: Partial nucleic acid sequence and complete deduced protein sequence of mouse SR-p70c (corresponding to SEQ ID No. 7).

Figure 8: Partial nucleic acid sequence and partially deduced protein sequence of mouse SR-p70a (corresponding to SEQ ID No. 9).

Figure 9: Multialignment of the proteins deduced from monkey (a and b), human (a) and mouse (a and c) SR-p70 cDNAs.

Figure 10a: Immunoblot of the SR-p70 protein.

Figure 10b: Detection of the endogenous SR-p70 protein.

Figure 11: Chromosomal localization of the human SR-p70 gene. The signal appears on chromosome 1, in the p36 region.

Figure 12: Genomic structure of the SR-p70 gene and

comparison with that of the p53 gene. The human protein sequences of SR-p70a (upper line of the alignment) and of p53 (lower line) are divided up into peptides on the basis of the respective exons from which they are encoded. The figures beside the arrows correspond to the numbering of the corresponding exons.

Figure 13: Human genomic sequence of SR-p70 from the 3′ end of intron 1 to the 5′ end of exon 3. The introns are boxed. At positions 123 and 133, two variable nucleic acid positions are localized (G → A at 123 and C → T at 133). The restriction sites for the enzyme StyI are underlined (position 130 in the case where a T is present instead of a C at position 133, position 542 and position 610). The arrows indicate the positions of the nucleic acid primers used in Example XI.

Figure 14: Nucleic acid comparison of the 5′ region of the human cDNAs of SR-p70d and of SR-p70a.

Figure 15: Multialignment of the nucleic acid sequences corresponding to human SR-p70a, b, d, e, and f.

Figure 16: Multialignment of the proteins deduced from human SR-p70 (a, b, d, e and f) cDNAs.

Figure 17: Partial nucleic acid sequence and partial deduced protein sequence of human SR-p70a. The two bases in bold characters correspond to two variable positions (see Figure 6). This sequence possesses a more complete non-coding 5′ region than the one presented in Figure 6.

Figure 18: Analysis of the SR-p70a transcripts after PCR amplification.

lane M: 1 kb ladder (GIBCO-BRL) molecular weight markers

lane 1: line HT29

lane 3: line SK-N-AS

lane 5: line UMR-32

lane 7: line U-373 MG

lane 9: line SW 480

lane 11: line CHP 212

lane 13: line SK-N-MC

lanes 2, 4, 6, 8, 10, 12, 14: negative controls corresponding to lanes 1, 3, 5, 7, 9, 11 and 13, respectively (absence of inverse transcriptase in the RT-PCR reaction).

Figure 19: A: Analysis by agarose gel electrophoresis of genomic fragments amplified by PCR (from the 3′ end of intron 1 to the 5′ end of exon 3). The numbering of the lanes corresponds to the numbering of the control population. Lane M: molecular weight markers (1 kb ladder).

B: Analysis identical to that of part A, after digestion of the same samples with the restriction enzyme StyI.

Figure 20: Diagrammatic representation with a partial restriction map of the plasmid pCDNA3 containing human SR-p70a.

EXAMPLE I

Cloning of SR-p70 cDNA from COS-3 cells

1. Culturing of COS-3 cells

COS-3 cells (African green monkey kidney cells transformed with the SV 40 virus T antigen) are cultured in DMEM medium (GIBCO-BRL reference 41 965-047) containing 2 mM L-glutamine and supplemented with 50 mg/l of gentamicin and 5% of foetal bovine serum (GIBCO-BRL reference 10231-074) to semi-confluence.

2. Preparation of the messenger RNA

a) **Extraction of the messenger RNA**

The cells are recovered in the following manner:

- the adherent cells are washed twice with PBS buffer (phosphate buffered saline, reference 04104040-GIBCO-BRL), then scraped off with a rubber scraper and centrifuged.

The cell pellet is suspended in the lysis buffer of the following composition: 4 M guanidine thiocyanate; 25 mM sodium citrate pH 7; 0.5% sarcosyl; 0.1 M β-mercaptoethanol. The suspension is sonicated using an Ultra-Turrax No. 231256 sonicator (Janke and Kundel) at maximum power for one minute. Sodium acetate pH 4 is added to a concentration of 0.2 M. The solution is extracted with one volume of a phenol/chloroform (5/1 v/v) mixture. The RNA contained in the aqueous phase is precipitated at -20°C using one volume of isopropanol. The pellet is resuspended in the lysis buffer. The solution is extracted again with a phenol/chloroform mixture and the RNA is precipitated with isopropanol. After washing of the pellet with 70% and then 100% ethanol, the RNA is resuspended in water.

b) Purification of the poly(A)$^+$ fraction of the RNA

Purification of poly(A)$^+$ fraction of the RNA is carried out using the DYNAL Dynabeads oligo(dT)$_{25}$ kit (reference 610.05) according to the protocol

recommended by the manufacturer. The principle is based on the use of superparamagnetic polystyrene beads to which an oligonucleotide poly(dT)$_{25}$ is attached. The poly(A)$^+$ fraction of the RNA is hybridized with the oligo(dT)$_{25}$ coupled to the beads, which are trapped on a magnetic support.

3. *Production of the complementary DNA library*

a) Preparation of the complementary DNA

From 0.5 μg of the poly(A)$^+$ RNA from COS-3 cells obtained at the end of step 2, the [^{32}P]dCTP-labelled single-stranded complementary DNA is prepared (the complementary DNA obtained possesses a specific activity of 3000 dpm/ng) with the synthetic primer of the following sequence (comprising a BamHI site):

5'<GATCCGGGCC CTTTTTTTTT TTT<3'

in a volume of 30 μl of buffer of composition: 50 mM Tris-HCl pH 8.3, 6 mM $MgCl_2$, 10 mM DDT, 40 mM KCl, containing 0.5 mM each of the deoxynucleotide triphosphates, 30 μCi of [α-^{32}P]dCTP and 30 U of RNasin (Promega). After one hour of incubation at 37°C, then 10 minutes at 50°C, then 10 minutes again at 37°C, with 200 units of the enzyme reverse transcriptase RNase H$^-$ (GIBCO-BRL reference 8064A), 4 μl of EDTA are added.

b) Alkaline hydrolysis of the RNA template

6 μl of 2N NaOH solution are added and the mixture is then incubated for 5 minutes at 65°C.

c) Purification on a Sephacryl S-400 column

In order to remove the synthetic primer, the complementary DNA is purified on a column of 1 ml of Sephacryl S-400 (Pharmacia) equilibrated in TE buffer.

The first two radioactive fractions are pooled and precipitated with 1/10 volume of 10 M ammonium acetate solution and 2.5 volumes of ethanol, this being done after extraction with one volume of chloroform.

d) Homopolymer addition of dG

The complementary DNA is elongated at the 3′ end with a dG tail with 20 units of the enzyme terminal transferase (Pharmacia 27073001). The mixture is incubated in 20 μl of buffer of composition: 30 mM Tris-HCl pH 7.6, 1 mM cobalt chloride, 140 mM cacodylic acid, 0.1 mM DTT, 1 mM dGTP, for 15 minutes at 37°C, and 2 μl of 0.5 M EDTA are then added.

e) Steps b) and c) are repeated again

f) Pairing of the cloning vector pSE1 (EP 506,574) and the complementary DNA in the presence of the adaptor.

The mixture is centrifuged, the pellet is dissolved in 33 μl of TE buffer, 5 μl (125 ng) of cloning vector pSE1, 1 μl (120 ng) of the adaptor of the following sequence (comprising an ApaI site):

5′AAAAAAAAAAAAAAGGGCCCG3′

and 10 μl of 200 mM NaCl solution are added, and the reaction mixture is incubated for 5 minutes at 65°C and then allowed to cool to room temperature.

g) Ligation

The cloning vector and the single-stranded cDNA are ligated in a volume of 100 μl with 32.5 units of the enzyme phage T4 DNA ligase (Pharmacia reference 270 87002) overnight at 15°C in a buffer of composition: 50 mM Tris-HCl pH 7.5, 10 mM $MgCl_2$, 1 mM ATP.

h) Synthesis of the second strand of the cDNA

The proteins are removed by phenol extraction followed by chloroform extraction, and 1/10 volume of 10 mM ammonium acetate solution and then 2.5 volumes of ethanol are then added. The mixture is centrifuged, the pellet is dissolved in a buffer of composition 33 mM Tris-acetate pH 7.9, 62.5 mM potassium acetate, 1 mM magnesium acetate and 1 mM dithiothreitol (DTT), and the second strand of complementary DNA is synthesized in a volume of 30 μl with 30 units of the enzyme phage T4 DNA polymerase (Pharmacia reference 270718) and a

mixture of 1 mM the four deoxynucleotide triphosphates dATP, dCTP, dGTP and dTTP as well as two units of phage T4 gene 32 protein (Pharmacia reference 27-0213) for one hour at 37°C. The mixture is extracted with phenol and the traces of phenol are removed with a column of polyacrylamide P10 (Biogel P10-200-400 mesh - reference 15011050 - Biorad).

i) Transformation by electroporation

E. coli MC 1061 cells are transformed with the recombinant DNA obtained above by electroporation using a Biorad Gene Pulser apparatus (Biorad) used at 2.5 kV under the conditions specified by the manufacturer, and the bacteria are then grown for one hour in the medium known as LB medium (Sambrook *op. cit.*) of composition: bactotryptone 10 g/l; yeast extract 5 g/l; NaCl 10 g/l.

The number of independent clones is determined by plating out a 1/1000 dilution of the transformation after the first hour of incubation on a dish of LB medium with the addition of 1.5% of agar (w/v) and 100 μg/ml of ampicillin, hereinafter referred to as LB agar medium. The number of independent clones is 1 million.

j) Analysis of the cDNAs of the library

In the context of the analysis of individual clones of the library by nucleic acid sequencing of the 5′ region of the cDNAs, one clone, designated SR-p70a, was shown to exhibit a partial homology with the cDNA of the already known protein, the p53 protein (Genbank X 02469 and X 16384) (Figure 1). The sequences were produced with the United States Biochemical kit (reference 70770) and/or the Applied Biosystems kit (references 401434 and/or 401628), which use the method of Sanger et al., Proc. Natl. Acad. Sci. USA; 1977, *14*, 5463-5467. The plasmid DNA is prepared from the WIZARD minipreparation kit (Promega reference A7510). The primers used are 16- to 22-mer oligonucleotides, complementary either to

the vector pSE1 in the region immediately at the 5' end of the cDNA, or to the sequence of the cDNA.

A second cDNA was isolated from the same library by screening, in a manner similar to the technique described in EXAMPLE III.3) below, with a fragment of SR-p70a the DNA labelled with ^{32}P with the BRL "Random Primers DNA labelling systems" kit (reference 18187-013). The hybridization and washing buffers are treated by adding 50% of formamide. The last wash is carried out in 0.1 × SSC/0.1% SDS at 60°C. This second sequence (SR-p70b cDNA) is identical to the first but an internal fragment has been deleted from it (Figure 3).

The two SR-p70 cDNAs, of length 2874 nucleotides (SR-p70a) and 2780 nucleotides (SR-p70b), correspond to the products of a single gene, an alternative splicing bringing about a deletion of 94 bases between nucleotides 1637 and 1732 and a premature termination of the corresponding encoded protein. The proteins deduced from the two cDNAs possess 637 amino acids and 499 amino acids, respectively (Figures 4 and 5).

EXAMPLE II

Obtaining of the sequence and cloning of the cDNA of the SR-p70a protein from HT-29 (human colon adenocarcinoma) cells

1) Culturing of HT-29 cells

The cells are cultured in McCoy's 5 medium (GIBCO 26600-023) with the addition of 10% of foetal calf serum (GIBCO 10081-23) and 50 mg/l of gentamicin, to semi-confluence.

2) Preparation of the complementary DNA

The messenger RNA is prepared as described in EXAMPLE I.2. The cDNA is prepared in a manner similar to that described in EXAMPLE I.3, with 5 μg of total messenger RNA, using a poly$(T)_{12}$ primer. The reaction is

not interrupted with EDTA.

3) Specific amplification of the human cDNA by the so-called PCR technique

The polymerization is carried out with 4 μl of cDNA in 50 μl final with the buffer of the following composition: 10 mM Tris-HCl pH 8.3, 2.5 mM $MgCl_2$, 50 mM KCl in the presence of 10% DMSO, 0.5 mM dNTP, 4 μg/ml of each of the two nucleic acid primers and 2.5 units of TAQ DNA polymerase (Boehringer). The primer pairs were selected on the basis of the nucleic acid sequence of the COS-3 SR-p70 clone, in particular upstream of the translation initiation ATG and downstream of the translation stop TGA, and are of the following compositions:

sense primer: ACT <u>GGT ACC</u> GCG AGC TGC CCT CGG AG
Kpn I restriction site

antisense primer: GAC <u>TCT AGA</u> GGT TCT GCA GGT GAC TCA G
Xba I restriction site

The reaction is carried out for 30 cycles of 94°C/1 minute, 54-60°C/1 minute 30 seconds and 72°C/1 minute 30 seconds, followed by a final cycle of 72°C/6 minutes.

4) Obtaining of the sequence of the human cDNA

In a first step, the PCR product is removed from the oligonucleotides on a column of Sephacryl S-400, and then desalted by exclusion chromatography on a column of polyacrylamide P10 (Biorad reference 1504144). The sequencing reactions are carried out using the Applied Biosystems kit (reference 401628) with oligonucleotides specific for the cDNA. The sequence obtained is very similar to that of monkey SR-p70a, and the deduced protein contains 636 amino acids (Figure 6).

In a similar manner, other sequences originating from human lines or tissues were obtained for the coding

portion of human SR-p70, in particular from the lung or pancreas. The proteins deduced from these sequences are identical to those obtained for the HT-29 line.

5) Cloning of the human cDNA into plasmid pCDNA3 (Invitrogen V 790-20)

The PCR product obtained in 3) and also the plasmid are digested with the two restriction enzymes Kpn I and Xba I and then purified after migration on a 1% agarose gel using the Geneclean kit (Bio 101 reference 3105). After ligation with 100 ng of insert and 10 ng of vector and transformation (technique described in EXAMPLE I.3.g and i), the recombinant clones are verified by sequencing using the Applied Biosystems kit mentioned above.

EXAMPLE III

Cloning of mouse SR-p70 cDNA from AtT-20 (pituitary tumour) cells

1) Cell culturing of the line AtT-20

The cells are cultured in Ham F10 medium (GIBCO 31550-023) with the addition of 15% of horse serum (GIBCO 26050-047), 2.5% of foetal calf serum (GIBCO 10081-073) and 50 mg/l of gentamicin, to semi-confluence.

2) Preparation of the complementary DNA library

The library is produced as described in EXAMPLE I. 2 and 3 from the cells cultured above.

3) Screening of the library

a) Preparation of the membranes

The clones of the library are plated out on LB agar medium (Petri dishes 150 mm in diameter) coated with Biodyne A membranes (PALL reference BNNG 132). After one night at 37°C, the clones are transferred by contact onto fresh membranes. The latter are treated by depositing them on 3 mm Whatman paper soaked with the following solutions: 0.5 N NaOH, 1.5 M NaCl for 5 minutes, then

0.5 M Tris-HCl pH 8, 1.5 M NaCl for 5 minutes. After treatment with proteinase K in the following buffer: 10 mM Tris-HCl pH 8, 10 mM EDTA, 50 mM NaCl, 0.1% SDS, 100 μg/ml proteinase K, for one hour at room temperature, the membranes are washed copiously in 2 × SSC (sodium citrate, NaCl), dried and then incubated in an oven under vacuum at 80°C for 20 minutes.

b) Preparation of the probe

On the basis of monkey and human SR-p70 cDNA sequences, a first sequence was produced on a fragment amplified from line AtT-20 mRNA as described in EXAMPLE II.3 and 4, with the oligomers of the following compositions:

sense primer: GCC ATG CCT GTC TAC AAG

antisense primer: ACC AGC TGG TTG ACG GAG.

On the basis of this sequence, an oligomeric probe specific for mouse was chosen and possesses the following composition:

GAG CAT GTG ACC GAC ATT G.

100 ng of the probe are labelled at the 3' end with 10 units of terminal transferase (Pharmacia) and 100 μCi of [α-^{32}P]dCTP 3000 Ci/mmol (Amersham reference PB 10205) in 10 μl of the following buffer: 30 mM Tris-HCl pH 7.6, 140 mM cacodylic acid, 1 mM $CoCl_2$, 0.1 mM DTT for 15 minutes at 37°C. The radiolabelled nucleotides not incorporated are removed on a column of polyacrylamide P10 (Biorad, reference 1504144). The probe obtained has a specific activity of approximately 5 × 10^8 dpm/μg.

c) Prehybridization and hybridization

The membranes prepared in a) are prehybridized for 30 minutes at 42°C in 6 × SSC, 5 × Denhart's, 0.1% SDS, and then hybridized for a few hours in the same buffer with the addition of the probe prepared in b) in the proportion of 10^6 dpm/ml.

d) Washing and exposure of the membranes

The membranes are washed twice at room temperature in 2 × SSC/0.1% SDS buffer and then for one hour at 56°C in 6 × SSC/0.1% SDS. The hybridized clones are visualized with KODAK XOMAT films. A positive clone

containing the mouse SR-p70 is selected and hereinafter designated as SR-p70c.

4) Sequencing of mouse SR-p70 and analysis of the sequence

The sequence is obtained using the Applied Biosystem kit (reference 401628). The protein sequence deduced from mouse SR-p70c cDNA (Figure 7) exhibits a very strong homology with the human and monkey sequences, except in the N-terminal portion which diverges strongly (see Figure 9). Using the so-called PCR technique in a similar manner to that described in EXAMPLE II.3 and 4, a second 5′ sequence (originating from the same AtT-20 library) was obtained (Figure 8). The deduced N-terminal protein sequence (sequence designated SR-p70a) is very similar to that deduced from human and monkey SR-p70 cDNAs (SR-p70a) (Figure 9). The line AtT-20 hence affords at least two SR-p70 transcripts. The latter 2 diverge in the N-terminal portion through different splicings.

EXAMPLE IV

1) Production of recombinant SR-p70 protein in E. coli

a) Construction of the expression plasmid

This consists in placing the COOH-terminal portion of the monkey SR-p70a protein, from the valine at position 427 to the COOH-terminal histidine at position 637, in fusion with the glutathione S-transferase (GST) of the plasmid vector pGEX-4T-3 (Pharmacia reference 27-4583). For this purpose, the corresponding insert of SR-p70a (position 1434 to 2066) was amplified by PCR with 10 ng of plasmid containing monkey SR-p70a cDNA. The nucleic acid primers are of the following composition:

sense primer: TTT <u>GGA TCC</u> GTC AAC CAG CTG GTG GGC CAG
BamHI restriction site

antisense primer: AAA <u>GTC GAC</u> GTG GAT CTC GGC CTC C.
Sal I site

The fragment obtained and also the vector are digested with the restriction enzymes BamHI and Sal I and cloning is carried out as described in EXAMPLE II.5. The selected clone is referred to as pG SR-p70.

b) Expression and purification of the GST-pSR-p70 fusion protein

This step was carried out using the "bulk GST purification module" kit (Pharmacia Reference 27-4570-01).

In outline, the recombinant clone was cultured at 37°C in one litre of 2 × YTA medium + 100 μg/ml ampicillin. At OD 0.8, expression is induced with 0.5 mM IPTG for 2 hours at 37°C. After centrifugation, the cell pellet is taken up in cold PBS and then sonicated by ultrasound. After the addition of 1% Triton X-100, the preparation is incubated for 30 minutes with agitation at room temperature. After centrifugation at 12,000 g for 10 minutes at 4°C, the supernatant is recovered. Purification is then carried out on a glutathione-Sepharose 4B affinity chromatography column. Binding and washing are carried out in PBS buffer and elution is carried out by competition with reduced glutathione. The final concentration is brought to 300 μg/ml of fusion protein.

2) Production of SR-p70a protein in COS-3 cells

COS-3 cells are transfected with pSE1 plasmid DNA into which monkey SR-p70a cDNA has been cloned (EXAMPLE I.1), or with the vector pSE1 plasmid DNA as control, by the DEAE-dextran technique: the COS-3 cells are inoculated at 5×10^5 cells per 6 cm dish in culture medium containing 5% of foetal bovine serum (EXAMPLE I.1). After culture, the cells are rinsed with PBS. 1 ml of the following mixture is added: medium containing 6.5 μg of DNA, 250 μg/ml of DEAE-dextran and 100 μM chloroquine. The cells are incubated at 37°C in 5% CO_2 for 4 to 5 hours. The medium is aspirated off, 2 ml of PBS containing 10% of DMSO are added and the cells are incubated for one minute, shaking the dishes gently. The

medium is aspirated off again and the cells are rinsed twice with PBS. The cells are then incubated at 37°C with medium containing 2% of foetal bovine serum for the period during which expression takes place, which is generally 3 days.

The SR-p70a protein is then analysed as described in EXAMPLE IV by immunoblotting.

EXAMPLE V

Preparation of specific antibodies

150 µg of proteins of the sample prepared according to EXAMPLE IV were used to immunize a rabbit (New Zealand male weighing 1.5 to 2 kg approximately). The immunizations were performed every 15 days according to the protocol described by Vaitukaitis, Methods in Enzymology, 1981, *73*, 46. At the first injection, one volume of antigenic solution is emulsified with one volume of Freund's complete adjuvant (Sigma reference 4258). Five boosters were administered in Freund's incomplete adjuvant (Sigma reference 5506).

EXAMPLE VI

Detection of the SR-p70 protein: Western immunoblotting

1) Materials used for immunoblotting

a) Cell lines used for immunoblotting

The following cell lines were cultured as described in the catalogue "Catalogue of cell lines and hybridomas, 7th edition, 1992" of the ATCC (American Type Culture Collection): COS-3, CV-1 (monkey kidney cell line), HT-29, U-373MG (human glioblastoma), MCF7 (human mammary adenocarcinoma), SKNAS (human neuroblastoma cultured under the same conditions as COS-3), SK-N-MC (human neuroblastoma), IMR-32 (human neuroblastoma), CHP212 (human neuroblastoma cultured under the same conditions as CV-1), Saos-2 (osteosarcoma), SK-OV-3 (ovarian adenocarcinoma) and SW 480 (human colon adenocarcinoma).

b) COS-3 cells transfected by SR-p70a cDNA

COS-3 cells were transfected as described in EXAMPLE IV.2. As a control, the cells were transfected with pSE1 plasmid DNA not containing recombinant SR-p70a cDNA.

2) Preparation of protein samples from a eukaryotic cell culture or from transfected cells

After culture, the cells are washed with PBS and then taken up in RIPA buffer (PBS with 1% NP40, 0.5% sodium deoxycholate, 0.5% SDS) supplemented with 10 μg/ml RNAse A, 20 μg/ml DNAse 1, 2 μg/ml aprotinin, 0.5 μg/ml leupeptin, 0.7 μg/ml pepstatin and 170 μg/ml PMSF. The cells are sonicated by ultrasound at 4°C and left for 30 minutes at 4°C. After microcentrifugation at 12,000 rpm, the supernatant is recovered. The protein concentration is measured by the Bradford method.

3) Western blotting

5 or 50 μg of proteins (50 μg for the cell lines and 5 μg for transfected cells) are placed in 0.2 volume of the following 6 × electrophoresis buffer: 0.35 mM Tris-HCl pH 6.8, 10.3% SDS, 36% glycerol, 0.6 mM DTT, 0.012% bromophenol blue. The samples are applied and run in a 10% SDS-PAGE gel (30:0.8 Bis) and then electrotransferred onto a nitrocellulose membrane.

4) Visualization with the antibody

The membrane is incubated for 30 minutes in TBST blocking buffer (10 mM Tris-HCl pH 8, 150 mM NaCl, 0.2% Tween 20) with the addition of 5% of milk (GIBCO - SKIM MILK) at room temperature. The membrane is brought into contact successively with the anti-SR-p70 (αSR-p70) antibody in the same buffer for 16 hours at 4°C, washed 3 times for 10 minutes with TBST and then incubated for one hour at 37°C with a second, anti-rabbit immunoglobulin antibody coupled to peroxidase (SIGMA A055). After three washes of 15 minutes, the visualization is performed using the ECL kit (Amersham

RPN2106) by chemiluminescence.

In parallel, the same samples were subjected to visualization with an anti-p53 (αp53) antibody (Sigma BP5312) followed by a second, anti-mouse immunoglobulin antibody.

5) Figures and results

Figure 10: Immunoblot of the SR-p70 protein

Figure 10a: Detection of the recombinant SR-p70 protein
- columns 1 and 3: COS-3 transfected by the vector pSE1.
- columns 2 and 4: COS-3 transfected by plasmid pSE1 containing SR-p70a cDNA.
- columns 1 and 2: visualization with the anti-SR-p70 (αSR-p70) antibody.
- columns 3 and 4: visualization with the anti-p53 (αp53) antibody.

Figure 10b: Detection of the endogenous SR-p70 protein
- columns 1: COS-3; 2: CV-1; 3: HT-29; 4: U-373 MG; 5: MCF7; 6: SKNAS; 7: SK-N-MC; 8: IMR-32; 9: CHP212; 10: Saos-2; 11: SK-OV-3 and 12: SW480.

A: Visualization with the αSR-p70 antibody
B: Visualization with the αp53 antibody.

The αSR-p70 antibody specifically recognizes the recombinant proteins (Figure 10a) and endogenous proteins (Figure 10b) and does not cross with p53. The analysis of human or monkey cell lines shows the SR-p70 protein, like p53, is generally weakly detectable. In contrast, when an accumulation of p53 exists, SR-p70 becomes, for its part also, more readily detectable (Figure 10b). A study by RT-PCR of the distribution of SR-p70 transcripts shows that the gene is expressed in all the cell types tested.

EXAMPLE VII

Cloning of the SR-p70 gene and chromosomal localization

1) Cloning of SR-p70 gene

The library used is a cosmid library prepared

in the EXAMPLE III.3, with an SR-p70 DNA fragment labelled with ^{32}P with the BRL "Random Primers DNA Labelling Systems" kit (reference 18187-013). The hybridization and washing buffers are treated by adding 50% of formaldehyde. The last wash is carried out in 0.1 x SSC/0.1% SDS at 60°C. In a similar manner, the SR-p70 gene was isolated from a library prepared with C57 black mouse genomic DNA.

An analysis and a partial sequencing of the clones demonstrate the presence of 14 exons with a structure close to that of the p53 gene, in particular in the central portion where the size and positioning of the exons are highly conserved (Figure 12). This structure was partially defined in mouse and in man.

As an example, the human genomic sequences of the 3′ region of intron 1, of exon 2, of intron 3 and of the 5′ region of exon 3 are presented in Figure 13.

2) Chromosomal localization of the SR-p70 gene in man

This was carried out with human SR-70 gene DNA using the technique described by R. Slim et al., Hum. Genet., 1991, *88*, 21-26. Fifty mitoses were analysed, more than 80% of which had double spots localized at 1p36 on both chromosomes and more especially at 1p36.2-1p36.3 (Figure 11). The identification of chromosome 1 and its orientation are based on the heterochromatin of the secondary constriction. The pictures were produced on a Zeiss Axiophot microscope, taken with a LHESA cooled CCD camera and treated with Optilab.

EXAMPLE VIII

A) Demonstration of an mRNA coding for a deduced human SR-p70 protein possessing both a shorter N-terminal end and a divergence.

1) Culturing of IMR-32 (human neuroblastoma) cells

The cells were cultured as described in the catalogue "Catalogue of cell lines and hybridomas, 7th edition, 1992" of the ATCC (American Type Culture Collection).

2) Preparation of the cDNA

The RNA is prepared as described in Example I.2.a. The cDNA is prepared in a manner similar to that described in Example I.3, with 5 μg total RNA in a final volume of 20 μl using a poly$(T)_{12}$ primer and with cold nucleotides. The reaction is not interrupted with EDTA.

3) Specific amplification of SR-p70 cDNA by the so-called PCR technique

The polymerization is carried out with 2 μl of cDNA in 50 μl final with the buffer of the following composition: 50 mM Tris-HCl pH 9.2, 16 mM $(NH_4)_2SO_4$, 1.75 mM $MgCl_2$, in the presence of 10% DMSO, 0.4 mM NTP, 100 ng of each of the two nucleic acid primers and 3.5 units of the mixture of TAQ and PWO polymerases (Boehringer Mannheim, ref. 1681 842).

The primer pair is of the following composition:

sense primer: AGGCCGGCGTGGGGAAG (position 16 to 32, Figure 6)
antisense primer: CTTGGCGATCTGGCAGTAG (position 503 to 485, Figure 6).

The reaction is carried out for 30 cycles at 95°C/30 seconds, 58°C/1 minute and 68°C/2 minutes 30 seconds, followed by a final cycle of 68°C/10 minutes.

The PCR product is subjected to electrophoresis on a 1% agarose gel (TAE buffer). After ethidium bromide staining, two major bands are revealed: a band approximately 490 bp in size (expected size (see Figure 6)) and an additional band approximately 700 bp in size. The latter is extracted from the gel using the "Geneclean" kit (Bio 101, ref 1001 400). After a desalting on a column of polyacrylamide P10 (Biorad, ref

15011050), the fragment is subjected to a further PCR amplification for 10 cycles as described above.

4) Determination of the sequence of the amplified product

In a first step, the PCR product is removed from the oligonucleotides on a column of Sephacryl S-400 (Pharmacia 17-0609-01) and then desalted on a column of P10. The sequencing reaction is carried out using the Applied Biosystems kit (ref. 401 628) (373 DNA sequencer) with the antisense primer.

The sequence obtained is identical to the SR-p70 cDNA sequence (Example II.4) with an insertion of 198 bp between positions 217 and 218 (Figure 14). The deduced N-terminal protein sequence (sequence designated SR-p70d) is 49 amino acids shorter, with a divergence of the first 13 amino acids (sequence ID No. 13). There is hence coexistence of at least two different SR-p70 transcripts as already described for the mouse AtT-20 line.

B) Cloning of human SR-p70 and demonstration of an mRNA coding for a deduced human SR-p70 protein possessing the same N-terminal end as SR-p70d and a divergence in the C-terminal portion

1) Specific amplification of SR-p70 cDNA by the so-called PCR technique

The amplification was carried out as described in EXAMPLE VIII.A from purified RNA of IMR-32 cells with the primer pair of the following composition:

sense primer: GCG GCC ACG ACC GTG AC (position 160 to 176, sequence ID No. 11)

antisense primer: GGC AGC TTG GGT CTC TGG (position 1993 to 1976, Figure 6).

After removal of the excess primers on an S400 column and desalting on a P10 column, 1 μl of the sample is subjected again to a PCR with the primer pair of the following composition:

sense primer: TAT <u>CTC GAG</u> CTG TAC GTC GGT GAC CCC
XhoI (position

263 to 280, sequence ID No. 11)

antisense primer: ATA TCT AGA TCA GTG GAT CTC GGC CTC
XbaI (position 1943 to 1926, Figure 6).

2) Cloning of the amplified product into plasmid pCDNA3

The PCR product obtained in 1) is desalted on a P10 column, digested with the restriction enzymes XhoI and XbaI and then cloned into plasmid pCDNA3 as described in EXAMPLE II.5. Two recombinant clones are sequenced using the Applied Biosystems kit with the oligonucleotides specific for SR-p70 cDNA.

The first sequence obtained corresponds to the complete sequence of the mRNA coding for SR-p70 described in EXAMPLE VIII.a. The deduced protein contains 587 amino acids (sequence ID No. 13 and Figure 16).

The second sequence obtained is identical to the SR-p70d cDNA sequence described above, but with two deletions, of 149 bp and of 94 bp between positions 1049 and 1050 on the one hand, and between positions 1188 and 1189 on the other hand (sequence ID No. 14 and Figure 15). The protein sequence deduced from this second sequence reveals a protein having an N-terminal portion 49 amino acids shorter, with a divergence in the first 13 amino acids as well as a divergence of protein sequence between amino acids 350 and 397 (sequence ID No. 15 and Figure 16) (sequence designated SR-p70e). The deduced protein contains 506 amino acids.

C) Demonstration of an mRNA coding for a deduced human SR-p70 protein possessing a shorter N-terminal end

1) Culturing of SK-N-SH (human neuroblastoma) cells

The cells are cultivated as described in the "Catalogue of cell lines and hybridomas, 7th edition, 1992" of the ATCC (American Type Culture Collection).

2) Preparation of the cDNA and amplification of SR-p70 cDNA by the so-called PCR technique

These steps are carried out as described in EXAMPLE VIII.A with the primer pair of the following composition:

sense primer: AGG GGA CGC AGC GAA ACC (position 128 to 145, Figure 17)

antisense primer: GGC AGC TTG GGT CTC TGG (position 1993 to 1976, Figure 6).

The sequencing is carried out with the Applied Biosystem kit with primers specific for SR-p70 cDNA, and reveals two cDNAs:

- a first cDNA corresponding to the mRNA coding for SR-p70a
- a second cDNA having a deletion of 98 bp between positions 24 and 25 (sequence ID No. 16 and Figure 15).

This deletion comprises the translation initiation ATG of SR-p70a. The protein deduced (designated SR-p70f) from this second cDNA possesses a translation initiation ATG downstream corresponding to an internal ATG of SR-p70a. The deduced protein hence contains 588 amino acids (sequence ID No. 17 and Figure 16) and is truncated with respect to the 48 N-terminal amino acids of SR-p70a.

D) Demonstration of an mRNA coding for human SR-p70b

1) Culturing of K562 cells

The cells are cultured as described in the "Catalogue of cell lines and hybridomas, 7th edition, 1992" of ATCC (American Type Culture Collection).

2) Preparation of the cDNA, amplification of SR-p70 cDNA by the so-called PCR technique and sequencing

These steps are carried out as described in EXAMPLE VIII.C.

The sequencing reveals two cDNAs:

A first cDNA corresponding to the mRNA coding for SR-p70a, and a second cDNA having a deletion of 94 bp

between positions 1516 and 1517 (sequence ID No. 18 and Figure 15). The deduced protein (designated SR-p70b) contains 199 amino acids and possesses a C-terminal sequence truncated by 137 amino acids relative to SR-p70a, with the last 4 amino acids divergent (sequence ID No. 19 and Figure 21).

This cDNA is similar to the one described in EXAMPLE I relating to monkey SR-p70b.

The molecules described in this example (EXAMPLE VIII.A, B, C and D) reveal SR-p70 variants which are the outcome of differential splicings of the primary mRNA, transcribed by the SR-p70 gene.

The SR-p70a is encoded by an mRNA composed of 14 exons (see EXAMPLE VII). This is the reference protein. SR-p70b is the outcome of an insertion between exons 3 and 4 and of the absence of exons 11 and 13. SR-p70f is the outcome of the absence of exon 2. This example describes the existance of SR-p70 variants non-exhaustively, with a strong probability of existence of other variants. Similarly, the existence of these variants described in this example, as well as SR-p70a, is not limited to the lines in which they have been demonstrated. In effect, studies performed by RT-PCR showed that these variants are to be found in the various lines studied.

Furthermore, the initiation methionine of SR-p70f corresponds to an internal methionine of SR-p70a, suggesting the possibility of initiation downstream on the mRNA coding for SR-p70a.

EXAMPLE IX

Obtaining a 5′ sequence of human SR-p70a mRNA

1) Amplification of the 5′ end of SR-p70 cDNA by PCR

The cell culturing and the preparations of total RNA and of cDNA are carried out as described in EXAMPLE VIII.1 and 2. The RNA template is hydrolysed by incubation for 5 minutes at 65°C after the addition of 4 μl of 500 mM EDTA and 4 μl of 2 N NaOH. The sample is

then desalted on a P10 column. The cDNA is elongated at the 3′ end with a dG tail as described in EXAMPLE I.3.d, in a final volume of 40 μl. After the addition of 4 μl of 500 mM EDTA and 4 μl of 2 N NaOH, the cDNA is incubated at 65°C for 3 minutes and then desalted on a P10 column. PCR amplification is carried out as described in EXAMPLE VIII.3 with 8 μl of cDNA and for 30 cycles with the primer pair of the following composition:

sense primer: C C C C C C C C C C C C C C N (where N equals G, A or T)

antisense primer: CCATCAGCTCCAGGCTCTC (position 1167 to 1149, Figure 6).

After removal of the excess primers on an S-400 column and desalting on a P10 column, 1 μl of the sample is subjected again to a PCR with the pair of the following composition:

sense primer: C C C C C C C C C C C C C C N

antisense primer: CCAGGACAGGCGCAGATG (position 928 to 911, Figure 6).

The sample, passed again through an S-400 column and a P10 column, is subjected to a third amplification for 20 cycles with the following pair:

sense primer: C C C C C C C C C C C C C C C N

antisense primer: CTTGGCGATCTGGCAGTAG (position 503 to 485, Figure 6).

2) Determination of the SR-p70 cDNA 5′ sequence

The sequence is produced as described in EXAMPLE VIII.4. This sequence reveals a non-coding 5′ region of at least 237 bases upstream of the initiation ATG of SR-p70a (Figure 17). By comparison of this sequence (obtained from the line IMR-32) with the one obtained from the line HT-29 in particular (Figure 6), two point differences (Figure 17: see bold characters) are revealed (G → A and C → T), positioned, respectively, at -20 and -30 from the initiation ATG of SR-p70a (Figures 6 and 17). This variability is located in exon 2 (Figure 13). It is not ruled out that this variability is also to be found within a coding frame as the outcome of an

alternative splicing as described in EXAMPLES III in mouse and VIII in man, or alternatively as the outcome of a translation initiation on a CTG (as has been demonstrated for FGFb (Proc. Natl. Acad. Sci USA, 1989, 86, 1836 - 1840)).

Similarly, it is not ruled out that this variability has a repercussion on the translation of SR-p70 or on the splicing of the primary RNA.

At all events, this variability, probably of allelic origin, may serve as a marker, either at genomic level (see EXAMPLE XI) or at mRNA level (see EXAMPLE X).

EXAMPLE X

1) Analysis by PCR of the transcriptional expression of SR-p70a in cell samples (RT-PCR)

Cell culturing (SK-N-AS, SK-N-MC, HT-29, U-373MG, SW480, IMR-32, CHP212) is carried out as described in Example VI.1.a (referred to the catalogue "Catalogue of cell lines and hybridomas, 7th edition 1992" of the ATCC).

The preparation of the cDNA and the PCR amplification are carried out as described in EXAMPLE VIII.2 and 3. The primer pair used is of the following composition:

sense primer: AGGGGACGCAGCGAAACC (position 128 to 145, Figure 17)

antisense primer: GGCAGCTTGGGTCTCTGG (position 1993 to 1976, Figure 6).

The samples are analysed by electrophoresis on a 1% agarose gel and visualization with ethidium bromide (Figure 18).

The size of the band obtained in the samples corresponds to the expected size (approximately 2 kb, Figures 6 and 17). The intensity of the bands obtained is reproducible. A reamplification of 1 μl of the sample under the same conditions for 20 cycles reveals a band in each of the samples.

2) Determination of the sequence of the amplified products

After passage of the samples through S-400 and P10 columns, sequencing is carried out on an Applied Biosystems sequencer 373 with the reference kit 401 628. The primers used are, inter alia, the following:

	position	Figure
AGGGGACGCAGCGAAACC	128 to 145	22
CTTGGCGATCTGGCAGTAG	503 to 485	6
GATGAGGTGGCTGGCTGGA	677 to 659	6
CCATCAGCTCCAGGCTCTC	1167 to 1149	6
TGGTCAGGTTCTGCAGGTG	1605 to 1587	6
GGCAGCTTGGGTCTCTGG	1993 to 1976	6

No protein difference in the SR-p70a was detected. However, sequences obtained reveal a double variability at positions -20 and -30 upstream of the initiation ATG of SR-p70a (Figures 6 and 17). This variability, probably of allelic origin, enables two classes of transcripts to be defined: a first class possessing a G at position -30 and a C at position -20 (class G^{-30}/C^{-20}) and a second class possessing a difference at two positions: an A at -30 and a T at -20 (class A^{-30}/T^{-20}).

First class: SK-N-AS, SK-N-MC, HT-29, U-373MG, SW480.

Second class: IMR-32, CHP212.

EXAMPLE XI

Analytical method of determination of the allelic distribution of the SR-p70 gene in a population of 10 persons

This allelic distribution is based on the allelic variability demonstrated in EXAMPLES IX and X:

- G^{-30}/C^{-20} allele possessing, respectively, a G and a C at positions -30 and -20 upstream of the initiation ATG of SR-p70a.
- A^{-30}/T^{-20} allele possessing, respectively, an A and

a T at the same positions.

This variability may be demonstrated by the use of restriction enzymes that differentiate the two alleles (Figure 13). As an example:

- Enzyme Bpl I having a cleavage site only on the G^{-30}/C^{-20} allele in the zone of interest (this site encompasses both variable positions).
- Enzyme StyI having a cleavage site only on the A^{-30}/T^{-20} allele in the zone of interest.

1) Genomic amplification of exon 2 by PCR

The polymerization reaction is carried out with 500 ng of purified genomic DNA, in 50 µl final with the conditions described in Example VIII.3.

The primer pair is of the following position:

Sense primer: CACCTACTCCAGGGATGC (position 1 to 18, Figure 13)
Antisense primer: AGGAAAATAGAAGCGTCAGTC (position 833 to 813, Figure 13).

The reaction is carried out for 30 cycles as described in EXAMPLE VIII.3.

After removal of the excess primer on an S-400 column and desalting on a P10 column, 1 µl of the sample is amplified again for 25 cycles under the same conditions with the following primer pair:

Sense primer: CAGGCCCACTTGCCTGCC (position 25 to 32, Figure 13)
Antisense primer: CTGTCCCCAAGCTGATGAG (position 506 to 488, Figure 13).

The amplified products are subjected to electrophoresis on a 1% agarose gel (Figure 19-A).

2) Digestion with the restriction enzyme StyI

The samples are desalted beforehand on a P10 column and then digested with the restriction enzyme StyI (BRL 15442-015) in the buffer of the following composition: 50 mM Tris-HCl pH 8, 100 mM NaCl, 10 mM $MgCl_2$, at 37°C for 30 min. The digestion products are analysed by electrophoresis on a 1% agarose gel (TAE buffer). Visualization is carried out by ethidium bromide

staining (Figure 19-B).

A band of 482 base pairs characterizes the G^{-30}/C^{-20} allele (Figures 13 and 19). The presence of a band of 376 base pairs and a band of 106 base pairs characterize the A^{-30}/T^{-20} allele (allele possessing a StyI cleavage site).

On the population of 10 persons, 2 persons exhibit the G^{-30}/C^{-20} and A^{-30}/T^{-20} alleles, the other 8 persons being homozygous with the G^{-30}/C^{-20} allele. The study of a fresh population of 9 persons demonstrated 3 heterozygous persons exhibiting the G^{-30}/C^{-20} and A^{-30}/T^{-20} alleles, the other 6 persons being homozygous for the G^{-30}/C^{-20} allele.

EXAMPLE XII

Test of reversion of transformation of the line SK-N-AS by transfection with SR-p70 cDNA

The expression vector used is described in EXAMPLE II.5 and shown diagrammatically in Figure 15. The method used is the so-called calcium phosphate method described by Graham et al. (Virology 1973, *54*, 2, 536-539). The line is inoculated in the proportion of 5×10^5 cells per dish 6 cm in diameter in 5 ml of the medium described in Example I.1. The cells are cultured at 37°C and with 5% CO_2 overnight. The transfection medium is prepared in the following manner: the following mixture is prepared by adding, in order, 1 ml of HEBS buffer (8 mg/ml NaCl, 370 μg/ml KCl, 125 μg/ml $Na_2HPO_4.2H_2O$, 1 mg/ml dextrose, 5 mg/ml Hepes pH 7.05), 10 μg of the plasmid to be transfected and 50 μl of 2.5 M $CaCl_2$ added dropwise. The transfection medium is left for 30 min at room temperature and then added dropwise to the medium contained in the culture dish. The cells are incubated for 5 to 6 hours at 37°C/5% CO_2. After the medium is aspirated off, 5 ml of fresh medium containing 2% of foetal bovine serum are added. After 48 hours at 37°C/5% CO_2, the cells are rinsed with PBS, detached by trypsinization, diluted in 10 ml of culture medium (5%

foetal bovine serum) and plated out in a dish 10 cm in diameter (the dilution may be adjusted in accordance with the efficiency of transfection). After a further incubation for 10 hours (the time for the cells to adhere), the cells are subjected to selection by adding G418 at a final concentration of 600 μg/ml Geneticin equivalent for 15 to 21 days (the medium is changed every day). The clones obtained are then rinsed with PBS, fixed in 70% ethanol, dried, stained with 1% crystal violet and then counted.

Four plasmid transfections were carried out in duplicate:

- plasmid pCDNA3 without insert
- plasmid pCDNA3/SR-p70 containing human SR-p70a cDNA
- plasmid pCDNA3/SR-p70 Mut containing SR-p70a cDNA possessing a mutation at position 293 AA (R → H) which is analogous to the mutation 273 (R → H) in the DNA-binding domain of p53
- control without plasmid.

The result is expressed as the number of clones per dish.

	Experiment 1	Experiment 2	Mean
pCDNA3	172	353	262
pCDNA3/SR-p70	13	8	10
pCDNA3/SR-p70 Mut	92	87	89
Absence of plasmid	1	3	2

The number of clones obtained by transfection with plasmid pCDNA3/SR-p70 is 25-fold less than the number of clones obtained with the control pCDNA3 and 9-fold less than the number of clones obtained with pCDNA3/SR-p70 Mut, indicating a mortality or an arrest of cell division of the cells transfected with SR-p70 cDNA. This result is not the consequence of a toxicity in view of the clones obtained with the mutated SR-p70 cDNA, but probably of an apoptosis as has been demonstrated for the

p53 protein (Koshland et al., Sciences, 1993, 262, 1953-1981).

EXAMPLE XIII

Biological role of the SR-p70 protein

The structural homology between the DNA-binding domain of p53 and the central region of the SR-p70 protein enables it to be inferred that SR-p70 is a transcription factor (see Figures 1 and 2). In effect, p53 (393 amino acids) consists of several functional domains. The N-terminal region (1-91 amino acids) is involved in the activation of transcription, and contains sites for interaction with different cellular and viral proteins. The central portion (amino acids 92 to 292) permits binding to the specific DNA sequences located in the promoter regions of certain genes (the majority of point mutations that inactivate p53 are localized in this region), and also possesses numerous sites for interaction with viral proteins which inhibit its activity. Finally, the last 100 amino acids of p53 are responsible for its oligomerization as well as for the regulation of the latter (Hainaut P., Current Opinion in Oncology, 1995, 7, 76-82; Prokocimer M., Blood, 1994, *84* No. 8, 2391-2411).

The sequence homology between p53 and SR-p70 is significant, in particular as regards the amino acids involved directly in the interaction with DNA, suggesting that SR-p70 binds to the p53 sites on DNA. These amino acids correspond very exactly to what are referred to as the "hot spots", amino acids frequently mutated in human tumours (SWISS PROT: SW: P53_human and Prokocimer M., Blood, 1994, *84* No. 8, 2391-2411). From this homology, it may be deduced that the SR-p70 protein exerts a control over the activity of the genes regulated by p53, either independently of the latter or by forming heterooligomers with it.

Consequently, like p53, the products of the SR-p70 gene must be involved in the control and regulation

of the cell cycle, causing the cycle to stop (momentarily or permanently), and the implementation of programmes such as DNA repair, differentiation or cell death. The likelihood of the existence of "p53-like" activities had been strongly felt with the demonstration in $p53^{-/-}$ mice of activities of DNA repair and cell death in response to ionizing radiations (Strasser *et al.*, Cell, 1994, *79*, 329-339). The authors of the present invention have localized the human SR-p70 gene in the telomeric region of the short arm of chromosome 1, precisely at 1p36.2-36.3, the smallest deleted region (SRO) common to a majority of neuroblastomas and of other types of tumours (melanomas and sarcomas) (White *et al.*, PNAS, 1995, *92*, 5520-5524). This region of loss of heterozygosity (LOH) defines the locus of a tumour-suppressing gene whose loss of activity is considered to be the cause of tumour formation. It is important to recall that this region is also subject to "maternal imprinting"; the maternal allele is preferentially lost in neuroblastomas having the 1p36 deletion (without amplification of N-Myc) (Caron *et al.*, Hum. Mol. Gen., 1995, *4*, 535-539). The wide-type SR-p70 gene introduced into neuroblastoma cells and expressed therein permits the reversion of their transformation. The loss of this anti-oncogenic activity is hence associated with the development of the tumour. The 1p36 region possesses a syngeneic homology with the distal segment of the mouse chromosome 4. In this region, the *curly tail (ct)* gene (Beier *et al.*, Mammalian Genome, 1995, *6*, 269-272) involved in congenital malformations of the neural tube (NTM: *spina bifida*, anencephaly, etc). The *ct* mouse is the best animal model for studying these malformations. It is accepted that these malformations result from abnormalities of cell proliferation. Bearing in mind the nature of the SR-p70 gene and its chromosomal localization, one of the hypotheses is that SR-p70 could be the human homologue of *ct* and that, on this basis, the detection of early mutations and chromosomal abnormalities affecting this gene should permit, for example, as an application, the identification of persons

at risk (0.5-1% of newborn babies affected by NTM) and the implementation of preventive treatments (Neumann *et al.*, Nature Genetics, 1994, *6*, 357-362; Di Vinci *et al.*, Int. J. Cancer, 1994, *59*, 422-426; Moll *et al.*, PNAS, 1995, *92*, 4407-4411; Chen *et al.*, Development, 1995, *121*, 681-691).

EXAMPLE XIV

Allelic study of the SR-p70 gene

The GC and AT alleles are readily identified by StyI restriction of the PCR products of exon 2 (see Example XI). Hence it was possible to determine in this way, in GC/AT heterozygous individuals bearing neuroblastoma tumours, the lost SR-p70 allele (GC or AT), in spite of the presence of contaminating healthy tissue.

Surprisingly, when the same analysis is carried out on the RNA, a single allele is demonstrated independently of the presence or otherwise of a deletion and, still more surprisingly, in spite of the presence of healthy tissue. This suggests that the imprint (differential expression of the two alleles) would also exist in the contaminating tissue.

In order to verify this, the same analysis was repeated on the RNA originating from blood cells of healthy GC/AT heterozygous individuals. Only one of the two types of transcript was detected also in these cells. This result confirms the observation made on the tumour samples regarding the existence of a generalized genetic imprint for the SR-p70 gene.

The implications of this discovery are important, since it enables it to be postulated that a single sporadic mutation inactivating the active SR-p70 allele will give rise to a loss of activity, this potentially occurring in all the tissues.

The absence of precise data on the biological function of SR-p70 does not enable the consequences of this loss of SR-p70 activity for the cell to be measured.

Nevertheless, its strong homology with the p53 tumour-suppressing protein, as well as the demonstration that SR-p70 is a transcription factor capable of utilizing the $P21^{waf}$ promoter, suggests a role of this protein in the control of the cell cycle and in differentiation.

Knudson and Meadows, 1980 (New Eng. J. Med. 302: 1254-56), consider the IV-S neuroblastomas to be a collection of non-malignant cells from the neural crest carrying a mutation which interferes with their normal differentiation.

It is conceivable that the loss of SR-p70 activity, like the loss of p53 control over the cell cycle, favours the appearance of cellular abnormalities such as aneuploidy, amplification (described in the case of neuroblastomas) and other genetic reorganizations capable of causing cell transformation (Livingstone et al., 1992, Cell 71:923-25; Yin et al. 1992, Cell 72:937-48; Cross et al. 1995, Science 267:1353-56; Fukasawa et al. 1996, Science 271:1744-47). Neuroblastomas might hence arise originally from a temporary or permanent loss of activity of SR-p70, thereby favouring the occurrence of oncogenic events and hence tumour progression.

In the case of the 1p36 constitutional deletion described by Biegel et al., 1993 (Am. J. Hum. Genet. 52:176-82), IV-S neuroblastoma does indeed occur and the gene affected is NBS-1 (SR-p70).

In conclusion, what is described for neuroblastomas might also apply to other types of tumours, in particular those associated with reorganization of the end of the short arm of chromosome 1 (Report 2 international workshop on human chr 1 mapping 1995, Cytogenetics and Cell Genet. 72:113-154). From a therapeutic standpoint, the involvement of SR-p70 in the occurrence of tumours should lead to the avoidance of the use of mutagenic agents in chemotherapy, bearing in mind the risks of cell transformation by these products, and to the use, in preference to these products, of non-mutagenic substances which stimulate differentiation.

Moreover, the frequency of occurrence of the GC

and AT alleles is as follows: in the population, Frequency(AT)=0.15, and on a sample of 25 (neuroblastoma) patients, F(AT)=0.30. These statistics indicate that the AT allele could be a predisposing factor.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: sanofi
(B) STREET: 32-34 rue Marbeuf
(C) CITY: PARIS
(E) COUNTRY: FRANCE
(F) POSTAL CODE (ZIP): 75008
(G) TELEPHONE: 01 53 77 40 00
(H) TELEFAX: 01 53 77 41 33

(ii) TITLE OF INVENTION: SR-p70

(iii) NUMBER OF SEQUENCES: 40

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2874 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Cebus apella

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 156..2066

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

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TGCCTCCCCG CCCGCGCACC CGCCCCGAGG CCTGTGCTCC TGCGAAGGGG ACGCAGCGAA      60

GCCGGGGCCC GCGCCAGGCC GGCCGGGACG GACGCCGATG CCCGGAGCTG CGACGGCTGC     120

AGAGCGAGCT GCCCTCGGAG GCCGGTGTGA GGAAG ATG GCC CAG TCC ACC ACC        173
                                       Met Ala Gln Ser Thr Thr
                                         1               5

ACC TCC CCC GAT GGG GGC ACC ACG TTT GAG CAC CTC TGG AGC TCT CTG       221
Thr Ser Pro Asp Gly Gly Thr Thr Phe Glu His Leu Trp Ser Ser Leu
                 10                  15                  20

GAA CCA GAC AGC ACC TAC TTC GAC CTT CCC CAG TCA AGC CGG GGG AAT       269
Glu Pro Asp Ser Thr Tyr Phe Asp Leu Pro Gln Ser Ser Arg Gly Asn
             25                  30                  35

AAT GAG GTG GTG GGT GGC ACG GAT TCC AGC ATG GAC GTC TTC CAC CTA       317
Asn Glu Val Val Gly Gly Thr Asp Ser Ser Met Asp Val Phe His Leu
         40                  45                  50

GAG GGC ATG ACC ACA TCT GTC ATG GCC CAG TTC AAT TTG CTG AGC AGC       365
Glu Gly Met Thr Thr Ser Val Met Ala Gln Phe Asn Leu Leu Ser Ser
     55                  60                  65                  70

ACC ATG GAC CAG ATG AGC AGC CGC GCT GCC TCG GCC AGC CCG TAC ACC       413
Thr Met Asp Gln Met Ser Ser Arg Ala Ala Ser Ala Ser Pro Tyr Thr
                     75                  80                  85
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CCG GAG CAC GCC GCC AGC GTG CCC ACC CAT TCA CCC TAC GCA CAG CCC       461
Pro Glu His Ala Ala Ser Val Pro Thr His Ser Pro Tyr Ala Gln Pro
             90                  95                 100

AGC TCC ACC TTC GAC ACC ATG TCG CCC GCG CCT GTC ATC CCC TCC AAC       509
Ser Ser Thr Phe Asp Thr Met Ser Pro Ala Pro Val Ile Pro Ser Asn
        105                 110                 115

ACC GAC TAT CCC GGA CCC CAC CAC TTC GAG GTC ACT TTC CAG CAG TCC       557
Thr Asp Tyr Pro Gly Pro His His Phe Glu Val Thr Phe Gln Gln Ser
    120                 125                 130

AGC ACG GCC AAG TCA GCC ACC TGG ACG TAC TCC CCA CTC TTG AAG AAA       605
Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Pro Leu Leu Lys Lys
135                 140                 145                 150

CTC TAC TGC CAG ATC GCC AAG ACA TGC CCC ATC CAG ATC AAG GTG TCC       653
Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys Val Ser
                155                 160                 165

GCC CCA CCG CCC CCG GGC ACC GCC ATC CGG GCC ATG CCT GTC TAC AAG       701
Ala Pro Pro Pro Pro Gly Thr Ala Ile Arg Ala Met Pro Val Tyr Lys
            170                 175                 180

AAG GCG GAG CAC GTG ACC GAC ATC GTG AAG CGC TGC CCC AAC CAC GAG       749
Lys Ala Glu His Val Thr Asp Ile Val Lys Arg Cys Pro Asn His Glu
        185                 190                 195

CTC GGG AGG GAC TTC AAC GAA GGA CAG TCT GCC CCA GCC AGC CAC CTC       797
Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser Ala Pro Ala Ser His Leu
    200                 205                 210

ATC CGT GTG GAA GGC AAT AAT CTC TCG CAG TAT GTG GAC GAC CCT GTC       845
Ile Arg Val Glu Gly Asn Asn Leu Ser Gln Tyr Val Asp Asp Pro Val
215                 220                 225                 230

ACC GGC AGG CAG AGC GTC GTG GTG CCC TAT GAG CCA CCA CAG GTG GGG       893
Thr Gly Arg Gln Ser Val Val Val Pro Tyr Glu Pro Pro Gln Val Gly
                235                 240                 245

ACA GAA TTC ACC ACC ATC CTG TAC AAC TTC ATG TGT AAC AGC AGC TGT       941
Thr Glu Phe Thr Thr Ile Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys
            250                 255                 260

GTG GGG GGC ATG AAC CGA CGG CCC ATC CTC ATC ATC ATC ACC CTG GAG       989
Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Ile Thr Leu Glu
        265                 270                 275

ACG CGG GAT GGG CAG GTG CTG GGC CGC CGG TCC TTC GAG GGC CGC ATC      1037
Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Ser Phe Glu Gly Arg Ile
    280                 285                 290

TGC GCC TGT CCT GGC CGC GAC CGA AAA GCC GAT GAG GAC CAC TAC CGG      1085
Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp His Tyr Arg
295                 300                 305                 310

GAG CAG CAG GCC TTG AAT GAG AGC TCC GCC AAG AAC GGG GCT GCC AGC      1133
Glu Gln Gln Ala Leu Asn Glu Ser Ser Ala Lys Asn Gly Ala Ala Ser
                315                 320                 325

AAG CGC GCC TTC AAG CAG AGT CCC CCT GCC GTC CCC GCC CTG GGC CCG      1181
Lys Arg Ala Phe Lys Gln Ser Pro Pro Ala Val Pro Ala Leu Gly Pro
            330                 335                 340

GGT GTG AAG AAG CGG CGG CAC GGA GAC GAG GAC ACG TAC TAC CTG CAG      1229
Gly Val Lys Lys Arg Arg His Gly Asp Glu Asp Thr Tyr Tyr Leu Gln
        345                 350                 355

GTG CGA GGC CGC GAG AAC TTC GAG ATC CTG ATG AAG CTG AAG GAG AGC      1277
Val Arg Gly Arg Glu Asn Phe Glu Ile Leu Met Lys Leu Lys Glu Ser
    360                 365                 370
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CTG GAG CTG ATG GAG TTG GTG CCG CAG CCG CTG GTA GAC TCC TAT CGG         1325
Leu Glu Leu Met Glu Leu Val Pro Gln Pro Leu Val Asp Ser Tyr Arg
375                 380                 385                 390

CAG CAG CAG CAG CTC CTA CAG AGG CCG AGT CAC CTA CAG CCC CCA TCC         1373
Gln Gln Gln Gln Leu Leu Gln Arg Pro Ser His Leu Gln Pro Pro Ser
                395                 400                 405

TAC GGG CCG GTC CTC TCG CCC ATG AAC AAG GTG CAC GGG GGC GTG AAC         1421
Tyr Gly Pro Val Leu Ser Pro Met Asn Lys Val His Gly Gly Val Asn
            410                 415                 420

AAG CTG CCC TCC GTC AAC CAG CTG GTG GGC CAG CCT CCC CCG CAC AGC         1469
Lys Leu Pro Ser Val Asn Gln Leu Val Gly Gln Pro Pro Pro His Ser
        425                 430                 435

TCG GCA GCT ACA CCC AAC CTG GGA CCT GTG GGC TCT GGG ATG CTC AAC         1517
Ser Ala Ala Thr Pro Asn Leu Gly Pro Val Gly Ser Gly Met Leu Asn
    440                 445                 450

AAC CAC GGC CAC GCA GTG CCA GCC AAC AGC GAG ATG ACC AGC AGC CAC         1565
Asn His Gly His Ala Val Pro Ala Asn Ser Glu Met Thr Ser Ser His
455                 460                 465                 470

GGC ACC CAG TCC ATG GTC TCG GGG TCC CAC TGC ACT CCG CCA CCC CCC         1613
Gly Thr Gln Ser Met Val Ser Gly Ser His Cys Thr Pro Pro Pro Pro
                475                 480                 485

TAC CAC GCC GAC CCC AGC CTC GTC AGT TTT TTA ACA GGA TTG GGG TGT         1661
Tyr His Ala Asp Pro Ser Leu Val Ser Phe Leu Thr Gly Leu Gly Cys
            490                 495                 500

CCA AAC TGC ATC GAG TAT TTC ACG TCC CAG GGG TTA CAG AGC ATT TAC         1709
Pro Asn Cys Ile Glu Tyr Phe Thr Ser Gln Gly Leu Gln Ser Ile Tyr
        505                 510                 515

CAC CTG CAG AAC CTG ACC ATC GAG GAC CTG GGG GCC CTG AAG ATC CCC         1757
His Leu Gln Asn Leu Thr Ile Glu Asp Leu Gly Ala Leu Lys Ile Pro
    520                 525                 530

GAG CAG TAT CGC ATG ACC ATC TGG CGG GGC CTG CAG GAC CTG AAG CAG         1805
Glu Gln Tyr Arg Met Thr Ile Trp Arg Gly Leu Gln Asp Leu Lys Gln
535                 540                 545                 550

GGC CAC GAC TAC GGC GCC GCC GCG CAG CAG CTG CTC CGC TCC AGC AAC         1853
Gly His Asp Tyr Gly Ala Ala Ala Gln Gln Leu Leu Arg Ser Ser Asn
                555                 560                 565

GCG GCC GCC ATT TCC ATC GGC GGC TCC GGG GAG CTG CAG CGC CAG CGG         1901
Ala Ala Ala Ile Ser Ile Gly Gly Ser Gly Glu Leu Gln Arg Gln Arg
            570                 575                 580

GTC ATG GAG GCC GTG CAC TTC CGC GTG CGC CAC ACC ATC ACC ATC CCC         1949
Val Met Glu Ala Val His Phe Arg Val Arg His Thr Ile Thr Ile Pro
        585                 590                 595

AAC CGC GGC GGC CCC GGC GCC GGC CCC GAC GAG TGG GCG GAC TTC GGC         1997
Asn Arg Gly Gly Pro Gly Ala Gly Pro Asp Glu Trp Ala Asp Phe Gly
    600                 605                 610

TTC GAC CTG CCC GAC TGC AAG GCC CGC AAG CAG CCC ATC AAG GAG GAG         2045
Phe Asp Leu Pro Asp Cys Lys Ala Arg Lys Gln Pro Ile Lys Glu Glu
615                 620                 625                 630

TTC ACG GAG GCC GAG ATC CAC TGAGGGGCCG GGCCCAGCCA GAGCCTGTGC            2096
Phe Thr Glu Ala Glu Ile His
                635

CACCGCCCAG AGACCCAGGC CGCCTCGCTC TCCTTCCTGT GTCCAAAACT GCCTCCGGAG       2156

GCAGGGCCTC CAGGCTGTGC CCGGGGAAAG GCAAGGTCCG GCCCATGCCC CGGCACCTCA       2216
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CCGGCCCCAG GAGAGGCCCA GCCACCAAAG CCGCCTGCGG ACAGCCTGAG TCACCTGCAG 2276

AACCTTCTGG AGCTGCCCTA ATGCTGGGCT TGCGGGGCAG GGGCCGGCCC ACTCTCAGCC 2336

CTGCCACTGC CGGGCGTGCT CCATGGCAGG CGTGGGTGGG GACCGCAGTG TCAGCTCCGA 2396

CCTCCAGGCC TCATCCTAGA GACTCTGTCA TCTGCCGATC AAGCAAGGTC CTTCCAGAGG 2456

AAAGAATCCT CTTCGCTGGT GGACTGCCAA AAAGTATTTT GCGACATCTT TTGGTTCTGG 2516

AGAGTGGTGA GCAGCCAAGC GACTGTGTCT GAAACACCGT GCATTTTCAG GGAATGTCCC 2576

TAACGGGCTG GGGACTCTCT CTGCTGGACT TGGGAGTGGC CTTTGCCCCC AGCACACTGT 2636

ATTCTGCGGG ACCGCCTCCT TCCTGCCCCT AACAACCACC AAAGTGTTGC TGAAATTGGA 2696

GAAAACTGGG GAAGGCGCAA CCCCTCCCAG GTGCGGGAAG CATCTGGTAC CGCCTCGGCC 2756

AGTGCCCCTC AGCCTGGCCA CAGTCACCTC TCCTTGGGGA ACCCTGGGCA GAAAGGGACA 2816

GCCTGTCCTT AGAGGACCGG AAATTGTCAA TATTTGATAA AATGATACCC TTTTCTAC 2874

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 637 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Met Ala Gln Ser Thr Thr Thr Ser Pro Asp Gly Gly Thr Thr Phe Glu
1 5 10 15

His Leu Trp Ser Ser Leu Glu Pro Asp Ser Thr Tyr Phe Asp Leu Pro
20 25 30

Gln Ser Ser Arg Gly Asn Asn Glu Val Val Gly Gly Thr Asp Ser Ser
35 40 45

Met Asp Val Phe His Leu Glu Gly Met Thr Thr Ser Val Met Ala Gln
50 55 60

Phe Asn Leu Leu Ser Ser Thr Met Asp Gln Met Ser Ser Arg Ala Ala
65 70 75 80

Ser Ala Ser Pro Tyr Thr Pro Glu His Ala Ala Ser Val Pro Thr His
85 90 95

Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Thr Met Ser Pro Ala
100 105 110

Pro Val Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His His Phe Glu
115 120 125

Val Thr Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr
130 135 140

Ser Pro Leu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro
145 150 155 160

Ile Gln Ile Lys Val Ser Ala Pro Pro Pro Pro Gly Thr Ala Ile Arg
165 170 175

Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Asp Ile Val Lys
180 185 190

Arg Cys Pro Asn His Glu Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser

195 200 205

Ala Pro Ala Ser His Leu Ile Arg Val Glu Gly Asn Asn Leu Ser Gln
210 215 220

Tyr Val Asp Asp Pro Val Thr Gly Arg Gln Ser Val Val Val Pro Tyr
225 230 235 240

Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Ile Leu Tyr Asn Phe
245 250 255

Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu
260 265 270

Ile Ile Ile Thr Leu Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg
275 280 285

Ser Phe Glu Gly Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala
290 295 300

Asp Glu Asp His Tyr Arg Glu Gln Gln Ala Leu Asn Glu Ser Ser Ala
305 310 315 320

Lys Asn Gly Ala Ala Ser Lys Arg Ala Phe Lys Gln Ser Pro Pro Ala
325 330 335

Val Pro Ala Leu Gly Pro Gly Val Lys Lys Arg Arg His Gly Asp Glu
340 345 350

Asp Thr Tyr Tyr Leu Gln Val Arg Gly Arg Glu Asn Phe Glu Ile Leu
355 360 365

Met Lys Leu Lys Glu Ser Leu Glu Leu Met Glu Leu Val Pro Gln Pro
370 375 380

Leu Val Asp Ser Tyr Arg Gln Gln Gln Gln Leu Leu Gln Arg Pro Ser
385 390 395 400

His Leu Gln Pro Pro Ser Tyr Gly Pro Val Leu Ser Pro Met Asn Lys
405 410 415

Val His Gly Gly Val Asn Lys Leu Pro Ser Val Asn Gln Leu Val Gly
420 425 430

Gln Pro Pro Pro His Ser Ser Ala Ala Thr Pro Asn Leu Gly Pro Val
435 440 445

Gly Ser Gly Met Leu Asn Asn His Gly His Ala Val Pro Ala Asn Ser
450 455 460

Glu Met Thr Ser Ser His Gly Thr Gln Ser Met Val Ser Gly Ser His
465 470 475 480

Cys Thr Pro Pro Pro Pro Tyr His Ala Asp Pro Ser Leu Val Ser Phe
485 490 495

Leu Thr Gly Leu Gly Cys Pro Asn Cys Ile Glu Tyr Phe Thr Ser Gln
500 505 510

Gly Leu Gln Ser Ile Tyr His Leu Gln Asn Leu Thr Ile Glu Asp Leu
515 520 525

Gly Ala Leu Lys Ile Pro Glu Gln Tyr Arg Met Thr Ile Trp Arg Gly
530 535 540

Leu Gln Asp Leu Lys Gln Gly His Asp Tyr Gly Ala Ala Ala Gln Gln
545 550 555 560

Leu Leu Arg Ser Ser Asn Ala Ala Ala Ile Ser Ile Gly Gly Ser Gly
565 570 575

Glu Leu Gln Arg Gln Arg Val Met Glu Ala Val His Phe Arg Val Arg

580 585 590

His Thr Ile Thr Ile Pro Asn Arg Gly Gly Pro Gly Ala Gly Pro Asp
595 600 605

Glu Trp Ala Asp Phe Gly Phe Asp Leu Pro Asp Cys Lys Ala Arg Lys
610 615 620

Gln Pro Ile Lys Glu Glu Phe Thr Glu Ala Glu Ile His
625 630 635

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2034 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Cebus apella

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 156..1652

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

TGCCTCCCCG CCCGCGCACC CGCCCCGAGG CCTGTGCTCC TGCGAAGGGG ACGCAGCGAA 60

GCCGGGGCCC GCGCCAGGCC GGCCGGGACG GACGCCGATG CCCGGAGCTG CGACGGCTGC 120

AGAGCGAGCT GCCCTCGGAG GCCGGTGTGA GGAAG ATG GCC CAG TCC ACC ACC 173
Met Ala Gln Ser Thr Thr
1 5

ACC TCC CCC GAT GGG GGC ACC ACG TTT GAG CAC CTC TGG AGC TCT CTG 221
Thr Ser Pro Asp Gly Gly Thr Thr Phe Glu His Leu Trp Ser Ser Leu
10 15 20

GAA CCA GAC AGC ACC TAC TTC GAC CTT CCC CAG TCA AGC CGG GGG AAT 269
Glu Pro Asp Ser Thr Tyr Phe Asp Leu Pro Gln Ser Ser Arg Gly Asn
25 30 35

AAT GAG GTG GTG GGT GGC ACG GAT TCC AGC ATG GAC GTC TTC CAC CTA 317
Asn Glu Val Val Gly Gly Thr Asp Ser Ser Met Asp Val Phe His Leu
40 45 50

GAG GGC ATG ACC ACA TCT GTC ATG GCC CAG TTC AAT TTG CTG AGC AGC 365
Glu Gly Met Thr Thr Ser Val Met Ala Gln Phe Asn Leu Leu Ser Ser
55 60 65 70

ACC ATG GAC CAG ATG AGC AGC CGC GCT GCC TCG GCC AGC CCG TAC ACC 413
Thr Met Asp Gln Met Ser Ser Arg Ala Ala Ser Ala Ser Pro Tyr Thr
75 80 85

CCG GAG CAC GCC GCC AGC GTG CCC ACC CAT TCA CCC TAC GCA CAG CCC 461
Pro Glu His Ala Ala Ser Val Pro Thr His Ser Pro Tyr Ala Gln Pro
90 95 100

AGC TCC ACC TTC GAC ACC ATG TCG CCC GCG CCT GTC ATC CCC TCC AAC 509
Ser Ser Thr Phe Asp Thr Met Ser Pro Ala Pro Val Ile Pro Ser Asn
105 110 115

ACC GAC TAT CCC GGA CCC CAC CAC TTC GAG GTC ACT TTC CAG CAG TCC 557
Thr Asp Tyr Pro Gly Pro His His Phe Glu Val Thr Phe Gln Gln Ser
120 125 130

AGC ACG GCC AAG TCA GCC ACC TGG ACG TAC TCC CCA CTC TTG AAG AAA 605

Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Pro Leu Leu Lys Lys
135 140 145 150

CTC TAC TGC CAG ATC GCC AAG ACA TGC CCC ATC CAG ATC AAG GTG TCC 653
Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys Val Ser
155 160 165

GCC CCA CCG CCC CCG GGC ACC GCC ATC CGG GCC ATG CCT GTC TAC AAG 701
Ala Pro Pro Pro Pro Gly Thr Ala Ile Arg Ala Met Pro Val Tyr Lys
170 175 180

AAG GCG GAG CAC GTG ACC GAC ATC GTG AAG CGC TGC CCC AAC CAC GAG 749
Lys Ala Glu His Val Thr Asp Ile Val Lys Arg Cys Pro Asn His Glu
185 190 195

CTC GGG AGG GAC TTC AAC GAA GGA CAG TCT GCC CCA GCC AGC CAC CTC 797
Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser Ala Pro Ala Ser His Leu
200 205 210

ATC CGT GTG GAA GGC AAT AAT CTC TCG CAG TAT GTG GAC GAC CCT GTC 845
Ile Arg Val Glu Gly Asn Asn Leu Ser Gln Tyr Val Asp Asp Pro Val
215 220 225 230

ACC GGC AGG CAG AGC GTC GTG GTG CCC TAT GAG CCA CCA CAG GTG GGG 893
Thr Gly Arg Gln Ser Val Val Val Pro Tyr Glu Pro Pro Gln Val Gly
235 240 245

ACA GAA TTC ACC ACC ATC CTG TAC AAC TTC ATG TGT AAC AGC AGC TGT 941
Thr Glu Phe Thr Thr Ile Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys
250 255 260

GTG GGG GGC ATG AAC CGA CGG CCC ATC CTC ATC ATC ATC ACC CTG GAG 989
Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Ile Thr Leu Glu
265 270 275

ACG CGG GAT GGG CAG GTG CTG GGC CGC CGG TCC TTC GAG GGC CGC ATC 1037
Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Ser Phe Glu Gly Arg Ile
280 285 290

TGC GCC TGT CCT GGC CGC GAC CGA AAA GCC GAT GAG GAC CAC TAC CGG 1085
Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp His Tyr Arg
295 300 305 310

GAG CAG CAG GCC TTG AAT GAG AGC TCC GCC AAG AAC GGG GCT GCC AGC 1133
Glu Gln Gln Ala Leu Asn Glu Ser Ser Ala Lys Asn Gly Ala Ala Ser
315 320 325

AAG CGC GCC TTC AAG CAG AGT CCC CCT GCC GTC CCC GCC CTG GGC CCG 1181
Lys Arg Ala Phe Lys Gln Ser Pro Pro Ala Val Pro Ala Leu Gly Pro
330 335 340

GGT GTG AAG AAG CGG CGG CAC GGA GAC GAG GAC ACG TAC TAC CTG CAG 1229
Gly Val Lys Lys Arg Arg His Gly Asp Glu Asp Thr Tyr Tyr Leu Gln
345 350 355

GTG CGA GGC CGC GAG AAC TTC GAG ATC CTG ATG AAG CTG AAG GAG AGC 1277
Val Arg Gly Arg Glu Asn Phe Glu Ile Leu Met Lys Leu Lys Glu Ser
360 365 370

CTG GAG CTG ATG GAG TTG GTG CCG CAG CCG CTG GTA GAC TCC TAT CGG 1325
Leu Glu Leu Met Glu Leu Val Pro Gln Pro Leu Val Asp Ser Tyr Arg
375 380 385 390

CAG CAG CAG CAG CTC CTA CAG AGG CCG AGT CAC CTA CAG CCC CCA TCC 1373
Gln Gln Gln Gln Leu Leu Gln Arg Pro Ser His Leu Gln Pro Pro Ser
395 400 405

TAC GGG CCG GTC CTC TCG CCC ATG AAC AAG GTG CAC GGG GGC GTG AAC 1421
Tyr Gly Pro Val Leu Ser Pro Met Asn Lys Val His Gly Gly Val Asn
410 415 420

AAG CTG CCC TCC GTC AAC CAG CTG GTG GGC CAG CCT CCC CCG CAC AGC 1469

Lys Leu Pro Ser Val Asn Gln Leu Val Gly Gln Pro Pro Pro His Ser
425 430 435

TCG GCA GCT ACA CCC AAC CTG GGA CCT GTG GGC TCT GGG ATG CTC AAC 1517
Ser Ala Ala Thr Pro Asn Leu Gly Pro Val Gly Ser Gly Met Leu Asn
440 445 450

AAC CAC GGC CAC GCA GTG CCA GCC AAC AGC GAG ATG ACC AGC AGC CAC 1565
Asn His Gly His Ala Val Pro Ala Asn Ser Glu Met Thr Ser Ser His
455 460 465 470

GGC ACC CAG TCC ATG GTC TCG GGG TCC CAC TGC ACT CCG CCA CCC CCC 1613
Gly Thr Gln Ser Met Val Ser Gly Ser His Cys Thr Pro Pro Pro Pro
475 480 485

TAC CAC GCC GAC CCC AGC CTC GTC AGG ACC TGG GGG CCC TGAAGATCCC 1662
Tyr His Ala Asp Pro Ser Leu Val Arg Thr Trp Gly Pro
490 495

CGAGCAGTAT CGCATGACCA TCTGGCGGGG CCTGCAGGAC CTGAAGCAGG GCCACGACTA 1722

CGGCGCCGCC GCGCAGCAGC TGCTCCGCTC CAGCAACGCG GCCGCCATTT CCATCGGCGG 1782

CTCCGGGGAG CTGCAGCGCC AGCGGGTCAT GGAGGCCGTG CACTTCCGCG TGCGCCACAC 1842

CATCACCATC CCCAACCGCG GCGGCCCCGG CGCCGGCCCC GACGAGTGGG CGGACTTCGG 1902

CTTCGACCTG CCCGACTGCA AGGCCCGCAA GCAGCCCATC AAGGAGGAGT TCACGGAGGC 1962

CGAGATCCAC TGAGGGGCCG GGCCCAGCCA GAGCCTGTGC CACCGCCCAG AGACCCAGGC 2022

CGCCTCGCTC TC 2034

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 499 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Met Ala Gln Ser Thr Thr Thr Ser Pro Asp Gly Gly Thr Thr Phe Glu
1 5 10 15

His Leu Trp Ser Ser Leu Glu Pro Asp Ser Thr Tyr Phe Asp Leu Pro
20 25 30

Gln Ser Ser Arg Gly Asn Asn Glu Val Val Gly Gly Thr Asp Ser Ser
35 40 45

Met Asp Val Phe His Leu Glu Gly Met Thr Thr Ser Val Met Ala Gln
50 55 60

Phe Asn Leu Leu Ser Ser Thr Met Asp Gln Met Ser Ser Arg Ala Ala
65 70 75 80

Ser Ala Ser Pro Tyr Thr Pro Glu His Ala Ala Ser Val Pro Thr His
85 90 95

Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Thr Met Ser Pro Ala
100 105 110

Pro Val Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His His Phe Glu
115 120 125

Val Thr Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr
130 135 140

```
Ser Pro Leu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro
145                 150                 155                 160

Ile Gln Ile Lys Val Ser Ala Pro Pro Pro Pro Gly Thr Ala Ile Arg
                165                 170                 175

Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Asp Ile Val Lys
            180                 185                 190

Arg Cys Pro Asn His Glu Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser
        195                 200                 205

Ala Pro Ala Ser His Leu Ile Arg Val Glu Gly Asn Asn Leu Ser Gln
    210                 215                 220

Tyr Val Asp Asp Pro Val Thr Gly Arg Gln Ser Val Val Val Pro Tyr
225                 230                 235                 240

Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Ile Leu Tyr Asn Phe
                245                 250                 255

Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu
            260                 265                 270

Ile Ile Ile Thr Leu Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg
        275                 280                 285

Ser Phe Glu Gly Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala
    290                 295                 300

Asp Glu Asp His Tyr Arg Glu Gln Gln Ala Leu Asn Glu Ser Ser Ala
305                 310                 315                 320

Lys Asn Gly Ala Ala Ser Lys Arg Ala Phe Lys Gln Ser Pro Pro Ala
                325                 330                 335

Val Pro Ala Leu Gly Pro Gly Val Lys Lys Arg Arg His Gly Asp Glu
            340                 345                 350

Asp Thr Tyr Tyr Leu Gln Val Arg Gly Arg Glu Asn Phe Glu Ile Leu
        355                 360                 365

Met Lys Leu Lys Glu Ser Leu Glu Leu Met Glu Leu Val Pro Gln Pro
    370                 375                 380

Leu Val Asp Ser Tyr Arg Gln Gln Gln Gln Leu Leu Gln Arg Pro Ser
385                 390                 395                 400

His Leu Gln Pro Pro Ser Tyr Gly Pro Val Leu Ser Pro Met Asn Lys
                405                 410                 415

Val His Gly Gly Val Asn Lys Leu Pro Ser Val Asn Gln Leu Val Gly
            420                 425                 430

Gln Pro Pro Pro His Ser Ser Ala Ala Thr Pro Asn Leu Gly Pro Val
        435                 440                 445

Gly Ser Gly Met Leu Asn Asn His Gly His Ala Val Pro Ala Asn Ser
    450                 455                 460

Glu Met Thr Ser Ser His Gly Thr Gln Ser Met Val Ser Gly Ser His
465                 470                 475                 480

Cys Thr Pro Pro Pro Pro Tyr His Ala Asp Pro Ser Leu Val Arg Thr
                485                 490                 495

Trp Gly Pro
```

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2156 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 33..1940

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

```
GCGAGCTGCC CTCGGAGGCC GGCGTGGGGA AG ATG GCC CAG TCC ACC GCC ACC       53
                                    Met Ala Gln Ser Thr Ala Thr
                                     1               5

TCC CCT GAT GGG GGC ACC ACG TTT GAG CAC CTC TGG AGC TCT CTG GAA      101
Ser Pro Asp Gly Gly Thr Thr Phe Glu His Leu Trp Ser Ser Leu Glu
         10                  15                  20

CCA GAC AGC ACC TAC TTC GAC CTT CCC CAG TCA AGC CGG GGG AAT AAT      149
Pro Asp Ser Thr Tyr Phe Asp Leu Pro Gln Ser Ser Arg Gly Asn Asn
     25                  30                  35

GAG GTG GTG GGC GGA ACG GAT TCC AGC ATG GAC GTC TTC CAC CTG GAG      197
Glu Val Val Gly Gly Thr Asp Ser Ser Met Asp Val Phe His Leu Glu
 40                  45                  50                  55

GGC ATG ACT ACA TCT GTC ATG GCC CAG TTC AAT CTG CTG AGC AGC ACC      245
Gly Met Thr Thr Ser Val Met Ala Gln Phe Asn Leu Leu Ser Ser Thr
                 60                  65                  70

ATG GAC CAG ATG AGC AGC CGC GCG GCC TCG GCC AGC CCC TAC ACC CCA      293
Met Asp Gln Met Ser Ser Arg Ala Ala Ser Ala Ser Pro Tyr Thr Pro
             75                  80                  85

GAG CAC GCC GCC AGC GTG CCC ACC CAC TCG CCC TAC GCA CAA CCC AGC      341
Glu His Ala Ala Ser Val Pro Thr His Ser Pro Tyr Ala Gln Pro Ser
         90                  95                 100

TCC ACC TTC GAC ACC ATG TCG CCG GCG CCT GTC ATC CCC TCC AAC ACC      389
Ser Thr Phe Asp Thr Met Ser Pro Ala Pro Val Ile Pro Ser Asn Thr
    105                 110                 115

GAC TAC CCC GGA CCC CAC CAC TTT GAG GTC ACT TTC CAG CAG TCC AGC      437
Asp Tyr Pro Gly Pro His His Phe Glu Val Thr Phe Gln Gln Ser Ser
120                 125                 130                 135

ACG GCC AAG TCA GCC ACC TGG ACG TAC TCC CCG CTC TTG AAG AAA CTC      485
Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Pro Leu Leu Lys Lys Leu
                140                 145                 150

TAC TGC CAG ATC GCC AAG ACA TGC CCC ATC CAG ATC AAG GTG TCC ACC      533
Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys Val Ser Thr
            155                 160                 165

CCG CCA CCC CCA GGC ACT GCC ATC CGG GCC ATG CCT GTT TAC AAG AAA      581
Pro Pro Pro Pro Gly Thr Ala Ile Arg Ala Met Pro Val Tyr Lys Lys
        170                 175                 180

GCG GAG CAC GTG ACC GAC GTC GTG AAA CGC TGC CCC AAC CAC GAG CTC      629
Ala Glu His Val Thr Asp Val Val Lys Arg Cys Pro Asn His Glu Leu
    185                 190                 195

GGG AGG GAC TTC AAC GAA GGA CAG TCT GCT CCA GCC AGC CAC CTC ATC      677
Gly Arg Asp Phe Asn Glu Gly Gln Ser Ala Pro Ala Ser His Leu Ile
200                 205                 210                 215
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CGC GTG GAA GGC AAT AAT CTC TCG CAG TAT GTG GAT GAC CCT GTC ACC        725
Arg Val Glu Gly Asn Asn Leu Ser Gln Tyr Val Asp Asp Pro Val Thr
                220                 225                 230

GGC AGG CAG AGC GTC GTG GTG CCC TAT GAG CCA CCA CAG GTG GGG ACG        773
Gly Arg Gln Ser Val Val Val Pro Tyr Glu Pro Pro Gln Val Gly Thr
            235                 240                 245

GAA TTC ACC ACC ATC CTG TAC AAC TTC ATG TGT AAC AGC AGC TGT GTA        821
Glu Phe Thr Thr Ile Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val
        250                 255                 260

GGG GGC ATG AAC CGG CGG CCC ATC CTC ATC ATC ATC ACC CTG GAG ATG        869
Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Ile Thr Leu Glu Met
    265                 270                 275

CGG GAT GGG CAG GTG CTG GGC CGC CGG TCC TTT GAG GGC CGC ATC TGC        917
Arg Asp Gly Gln Val Leu Gly Arg Arg Ser Phe Glu Gly Arg Ile Cys
280                 285                 290                 295

GCC TGT CCT GGC CGC GAC CGA AAA GCT GAT GAG GAC CAC TAC CGG GAG        965
Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp His Tyr Arg Glu
                300                 305                 310

CAG CAG GCC CTG AAC GAG AGC TCC GCC AAG AAC GGG GCC GCC AGC AAG       1013
Gln Gln Ala Leu Asn Glu Ser Ser Ala Lys Asn Gly Ala Ala Ser Lys
            315                 320                 325

CGT GCC TTC AAG CAG AGC CCC CCT GCC GTC CCC GCC CTT GGT GCC GGT       1061
Arg Ala Phe Lys Gln Ser Pro Pro Ala Val Pro Ala Leu Gly Ala Gly
        330                 335                 340

GTG AAG AAG CGG CGG CAT GGA GAC GAG GAC ACG TAC TAC CTT CAG GTG       1109
Val Lys Lys Arg Arg His Gly Asp Glu Asp Thr Tyr Tyr Leu Gln Val
    345                 350                 355

CGA GGC CGG GAG AAC TTT GAG ATC CTG ATG AAG CTG AAA GAG AGC CTG       1157
Arg Gly Arg Glu Asn Phe Glu Ile Leu Met Lys Leu Lys Glu Ser Leu
360                 365                 370                 375

GAG CTG ATG GAG TTG GTG CCG CAG CCA CTG GTG GAC TCC TAT CGG CAG       1205
Glu Leu Met Glu Leu Val Pro Gln Pro Leu Val Asp Ser Tyr Arg Gln
                380                 385                 390

CAG CAG CAG CTC CTA CAG AGG CCG AGT CAC CTA CAG CCC CCG TCC TAC       1253
Gln Gln Gln Leu Leu Gln Arg Pro Ser His Leu Gln Pro Pro Ser Tyr
            395                 400                 405

GGG CCG GTC CTC TCG CCC ATG AAC AAG GTG CAC GGG GGC ATG AAC AAG       1301
Gly Pro Val Leu Ser Pro Met Asn Lys Val His Gly Gly Met Asn Lys
        410                 415                 420

CTG CCC TCC GTC AAC CAG CTG GTG GGC CAG CCT CCC CCG CAC AGT TCG       1349
Leu Pro Ser Val Asn Gln Leu Val Gly Gln Pro Pro Pro His Ser Ser
    425                 430                 435

GCA GCT ACA CCC AAC CTG GGG CCC GTG GGC CCC GGG ATG CTC AAC AAC       1397
Ala Ala Thr Pro Asn Leu Gly Pro Val Gly Pro Gly Met Leu Asn Asn
440                 445                 450                 455

CAT GGC CAC GCA GTG CCA GCC AAC GGC GAG ATG AGC AGC AGC CAC AGC       1445
His Gly His Ala Val Pro Ala Asn Gly Glu Met Ser Ser Ser His Ser
                460                 465                 470

GCC CAG TCC ATG GTC TCG GGG TCC CAC TGC ACT CCG CCA CCC CCC TAC       1493
Ala Gln Ser Met Val Ser Gly Ser His Cys Thr Pro Pro Pro Pro Tyr
            475                 480                 485

CAC GCC GAC CCC AGC CTC GTC AGT TTT TTA ACA GGA TTG GGG TGT CCA       1541
His Ala Asp Pro Ser Leu Val Ser Phe Leu Thr Gly Leu Gly Cys Pro
        490                 495                 500
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AAC TGC ATC GAG TAT TTC ACC TCC CAA GGG TTA CAG AGC ATT TAC CAC      1589
Asn Cys Ile Glu Tyr Phe Thr Ser Gln Gly Leu Gln Ser Ile Tyr His
    505                 510                 515

CTG CAG AAC CTG ACC ATT GAG GAC CTG GGG GCC CTG AAG ATC CCC GAG      1637
Leu Gln Asn Leu Thr Ile Glu Asp Leu Gly Ala Leu Lys Ile Pro Glu
520                 525                 530                 535

CAG TAC CGC ATG ACC ATC TGG CGG GGC CTG CAG GAC CTG AAG CAG GGC      1685
Gln Tyr Arg Met Thr Ile Trp Arg Gly Leu Gln Asp Leu Lys Gln Gly
                540                 545                 550

CAC GAC TAC AGC ACC GCG CAG CAG CTG CTC CGC TCT AGC AAC GCG GCC      1733
His Asp Tyr Ser Thr Ala Gln Gln Leu Leu Arg Ser Ser Asn Ala Ala
            555                 560                 565

ACC ATC TCC ATC GGC GGC TCA GGG GAA CTG CAG CGC CAG CGG GTC ATG      1781
Thr Ile Ser Ile Gly Gly Ser Gly Glu Leu Gln Arg Gln Arg Val Met
        570                 575                 580

GAG GCC GTG CAC TTC CGC GTG CGC CAC ACC ATC ACC ATC CCC AAC CGC      1829
Glu Ala Val His Phe Arg Val Arg His Thr Ile Thr Ile Pro Asn Arg
    585                 590                 595

GGC GGC CCA GGC GGC GGC CCT GAC GAG TGG GCG GAC TTC GGC TTC GAC      1877
Gly Gly Pro Gly Gly Gly Pro Asp Glu Trp Ala Asp Phe Gly Phe Asp
600                 605                 610                 615

CTG CCC GAC TGC AAG GCC CGC AAG CAG CCC ATC AAG GAG GAG TTC ACG      1925
Leu Pro Asp Cys Lys Ala Arg Lys Gln Pro Ile Lys Glu Glu Phe Thr
                620                 625                 630

GAG GCC GAG ATC CAC TGAGGGCCTC GCCTGGCTGC AGCCTGCGCC ACCGCCCAGA      1980
Glu Ala Glu Ile His
            635

GACCCAAGCT GCCTCCCCTC TCCTTCCTGT GTGTCCAAAA CTGCCTCAGG AGGCAGGACC    2040

TTCGGGCTGT GCCCGGGGAA AGGCAAGGTC CGGCCCATCC CCAGGCACCT CACAGGCCCC    2100

AGGAAAGGCC CAGCCACCGA AGCCGCCTGT GGACAGCCTG AGTCACCTGC AGAACC        2156
```

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 636 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

```
Met Ala Gln Ser Thr Ala Thr Ser Pro Asp Gly Gly Thr Thr Phe Glu
  1               5                  10                  15

His Leu Trp Ser Ser Leu Glu Pro Asp Ser Thr Tyr Phe Asp Leu Pro
             20                  25                  30

Gln Ser Ser Arg Gly Asn Asn Glu Val Val Gly Gly Thr Asp Ser Ser
         35                  40                  45

Met Asp Val Phe His Leu Glu Gly Met Thr Thr Ser Val Met Ala Gln
     50                  55                  60

Phe Asn Leu Leu Ser Ser Thr Met Asp Gln Met Ser Ser Arg Ala Ala
 65                  70                  75                  80

Ser Ala Ser Pro Tyr Thr Pro Glu His Ala Ala Ser Val Pro Thr His
                 85                  90                  95
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Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Thr Met Ser Pro Ala
            100                 105                 110

Pro Val Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His His Phe Glu
        115                 120                 125

Val Thr Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr
    130                 135                 140

Ser Pro Leu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro
145                 150                 155                 160

Ile Gln Ile Lys Val Ser Thr Pro Pro Pro Pro Gly Thr Ala Ile Arg
                165                 170                 175

Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Asp Val Val Lys
            180                 185                 190

Arg Cys Pro Asn His Glu Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser
        195                 200                 205

Ala Pro Ala Ser His Leu Ile Arg Val Glu Gly Asn Asn Leu Ser Gln
    210                 215                 220

Tyr Val Asp Asp Pro Val Thr Gly Arg Gln Ser Val Val Val Pro Tyr
225                 230                 235                 240

Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Ile Leu Tyr Asn Phe
                245                 250                 255

Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu
            260                 265                 270

Ile Ile Ile Thr Leu Glu Met Arg Asp Gly Gln Val Leu Gly Arg Arg
        275                 280                 285

Ser Phe Glu Gly Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala
    290                 295                 300

Asp Glu Asp His Tyr Arg Glu Gln Gln Ala Leu Asn Glu Ser Ser Ala
305                 310                 315                 320

Lys Asn Gly Ala Ala Ser Lys Arg Ala Phe Lys Gln Ser Pro Pro Ala
                325                 330                 335

Val Pro Ala Leu Gly Ala Gly Val Lys Lys Arg Arg His Gly Asp Glu
            340                 345                 350

Asp Thr Tyr Tyr Leu Gln Val Arg Gly Arg Glu Asn Phe Glu Ile Leu
        355                 360                 365

Met Lys Leu Lys Glu Ser Leu Glu Leu Met Glu Leu Val Pro Gln Pro
    370                 375                 380

Leu Val Asp Ser Tyr Arg Gln Gln Gln Gln Leu Leu Gln Arg Pro Ser
385                 390                 395                 400

His Leu Gln Pro Pro Ser Tyr Gly Pro Val Leu Ser Pro Met Asn Lys
                405                 410                 415

Val His Gly Gly Met Asn Lys Leu Pro Ser Val Asn Gln Leu Val Gly
            420                 425                 430

Gln Pro Pro Pro His Ser Ser Ala Ala Thr Pro Asn Leu Gly Pro Val
        435                 440                 445

Gly Pro Gly Met Leu Asn Asn His Gly His Ala Val Pro Ala Asn Gly
    450                 455                 460

Glu Met Ser Ser Ser His Ser Ala Gln Ser Met Val Ser Gly Ser His
465                 470                 475                 480
```

```
Cys Thr Pro Pro Pro Pro Tyr His Ala Asp Pro Ser Leu Val Ser Phe
                485                 490                 495

Leu Thr Gly Leu Gly Cys Pro Asn Cys Ile Glu Tyr Phe Thr Ser Gln
            500                 505                 510

Gly Leu Gln Ser Ile Tyr His Leu Gln Asn Leu Thr Ile Glu Asp Leu
        515                 520                 525

Gly Ala Leu Lys Ile Pro Glu Gln Tyr Arg Met Thr Ile Trp Arg Gly
    530                 535                 540

Leu Gln Asp Leu Lys Gln Gly His Asp Tyr Ser Thr Ala Gln Gln Leu
545                 550                 555                 560

Leu Arg Ser Ser Asn Ala Ala Thr Ile Ser Ile Gly Gly Ser Gly Glu
                565                 570                 575

Leu Gln Arg Gln Arg Val Met Glu Ala Val His Phe Arg Val Arg His
            580                 585                 590

Thr Ile Thr Ile Pro Asn Arg Gly Gly Pro Gly Gly Gly Pro Asp Glu
        595                 600                 605

Trp Ala Asp Phe Gly Phe Asp Leu Pro Asp Cys Lys Ala Arg Lys Gln
    610                 615                 620

Pro Ile Lys Glu Glu Phe Thr Glu Ala Glu Ile His
625                 630                 635
```

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2040 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Mus musculus

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 124..1890

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

```
TGATCTCCCT GTGGCCTGCA GGGGACTGAG CCAGGGAGTA GATGCCCTGA GACCCCAAGG      60

GACACCCAAG GAAACCTTGC TGGCTTTGAG AAAGGGATCG TCTCTCTCCT GCCCAAGAGA     120

AGC ATG TGT ATG GGC CCT GTG TAT GAA TCC TTG GGG CAG GCC CAG TTC       168
    Met Cys Met Gly Pro Val Tyr Glu Ser Leu Gly Gln Ala Gln Phe
      1               5                  10                  15

AAT TTG CTC AGC AGT GCC ATG GAC CAG ATG GGC AGC CGT GCG GCC CCG       216
Asn Leu Leu Ser Ser Ala Met Asp Gln Met Gly Ser Arg Ala Ala Pro
                 20                  25                  30

GCG AGC CCC TAC ACC CCG GAG CAC GCC GCC AGC GCG CCC ACC CAC TCG       264
Ala Ser Pro Tyr Thr Pro Glu His Ala Ala Ser Ala Pro Thr His Ser
             35                  40                  45

CCC TAC GCG CAG CCC AGC TCC ACC TTC GAC ACC ATG TCT CCG GCG CCT       312
Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Thr Met Ser Pro Ala Pro
         50                  55                  60

GTC ATC CCT TCC AAT ACC GAC TAC CCC GGC CCC CAC CAC TTC GAG GTC       360
```

```
Val Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His His Phe Glu Val
     65                  70                  75

ACC TTC CAG CAG TCG AGC ACT GCC AAG TCG GCC ACC TGG ACA TAC TCC       408
Thr Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser
 80                  85                  90                  95

CCA CTC TTG AAG AAG TTG TAC TGT CAG ATT GCT AAG ACA TGC CCC ATC       456
Pro Leu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile
                100                 105                 110

CAG ATC AAA GTG TCC ACA CCA CCA CCC CCG GGC ACG GCC ATC CGG GCC       504
Gln Ile Lys Val Ser Thr Pro Pro Pro Pro Gly Thr Ala Ile Arg Ala
            115                 120                 125

ATG CCT GTC TAC AAG AAG GCA GAG CAT GTG ACC GAC ATT GTT AAG CGC       552
Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Asp Ile Val Lys Arg
        130                 135                 140

TGC CCC AAC CAC GAG CTT GGA AGG GAC TTC AAT GAA GGA CAG TCT GCC       600
Cys Pro Asn His Glu Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser Ala
    145                 150                 155

CCG GCT AGC CAC CTC ATC CGT GTA GAA GGC AAC AAC CTC GCC CAG TAC       648
Pro Ala Ser His Leu Ile Arg Val Glu Gly Asn Asn Leu Ala Gln Tyr
160                 165                 170                 175

GTG GAT GAC CCT GTC ACC GGA AGG CAG AGT GTG GTT GTG CCG TAT GAA       696
Val Asp Asp Pro Val Thr Gly Arg Gln Ser Val Val Val Pro Tyr Glu
                180                 185                 190

CCC CCA CAG GTG GGA ACA GAA TTT ACC ACC ATC CTG TAC AAC TTC ATG       744
Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Ile Leu Tyr Asn Phe Met
            195                 200                 205

TGT AAC AGC AGC TGT GTG GGG GGC ATG AAT CGG AGG CCC ATC CTT GTC       792
Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Val
        210                 215                 220

ATC ATC ACC CTG GAG ACC CGG GAT GGA CAG GTC CTG GGC CGC CGG TCT       840
Ile Ile Thr Leu Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Ser
    225                 230                 235

TTC GAG GGT CGC ATC TGT GCC TGT CCT GGC CGT GAC CGC AAA GCT GAT       888
Phe Glu Gly Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp
240                 245                 250                 255

GAA GAC CAT TAC CGG GAG CAA CAG GCT CTG AAT GAA AGT ACC ACC AAA       936
Glu Asp His Tyr Arg Glu Gln Gln Ala Leu Asn Glu Ser Thr Thr Lys
                260                 265                 270

AAT GGA GCT GCC AGC AAA CGT GCA TTC AAG CAG AGC CCC CCT GCC ATC       984
Asn Gly Ala Ala Ser Lys Arg Ala Phe Lys Gln Ser Pro Pro Ala Ile
            275                 280                 285

CCT GCC CTG GGT ACC AAC GTG AAG AAG AGA CGC CAC GGG GAC GAG GAC      1032
Pro Ala Leu Gly Thr Asn Val Lys Lys Arg Arg His Gly Asp Glu Asp
        290                 295                 300

ATG TTC TAC ATG CAC GTG CGA GGC CGG GAG AAC TTT GAG ATC TTG ATG      1080
Met Phe Tyr Met His Val Arg Gly Arg Glu Asn Phe Glu Ile Leu Met
    305                 310                 315

AAA GTC AAG GAG AGC CTA GAA CTG ATG GAG CTT GTG CCC CAG CCT TTG      1128
Lys Val Lys Glu Ser Leu Glu Leu Met Glu Leu Val Pro Gln Pro Leu
320                 325                 330                 335

GTT GAC TCC TAT CGA CAG CAG CAG CAG CAG CAG CTC CTA CAG AGG CCG      1176
Val Asp Ser Tyr Arg Gln Gln Gln Gln Gln Gln Leu Leu Gln Arg Pro
                340                 345                 350

AGT CAC CTG CAG CCT CCA TCC TAT GGG CCC GTG CTC TCC CCA ATG AAC      1224
```

Ser His Leu Gln Pro Pro Ser Tyr Gly Pro Val Leu Ser Pro Met Asn
355 360 365

AAG GTA CAC GGT GGT GTC AAC AAA CTG CCC TCC GTC AAC CAG CTG GTG 1272
Lys Val His Gly Gly Val Asn Lys Leu Pro Ser Val Asn Gln Leu Val
370 375 380

GGC CAG CCT CCC CCG CAC AGC TCA GCA GCT GGG CCC AAC CTG GGG CCC 1320
Gly Gln Pro Pro Pro His Ser Ser Ala Ala Gly Pro Asn Leu Gly Pro
385 390 395

ATG GGC TCC GGG ATG CTC AAC AGC CAC GGC CAC AGC ATG CCG GCC AAT 1368
Met Gly Ser Gly Met Leu Asn Ser His Gly His Ser Met Pro Ala Asn
400 405 410 415

GGT GAG ATG AAT GGA GGC CAC AGC TCC CAG ACC ATG GTT TCG GGA TCC 1416
Gly Glu Met Asn Gly Gly His Ser Ser Gln Thr Met Val Ser Gly Ser
420 425 430

CAC TGC ACC CCG CCA CCC CCC TAT CAT GCA GAC CCC AGC CTC GTC AGT 1464
His Cys Thr Pro Pro Pro Pro Tyr His Ala Asp Pro Ser Leu Val Ser
435 440 445

TTT TTG ACA GGG TTG GGG TGT CCA AAC TGC ATC GAG TGC TTC ACT TCC 1512
Phe Leu Thr Gly Leu Gly Cys Pro Asn Cys Ile Glu Cys Phe Thr Ser
450 455 460

CAA GGG TTG CAG AGC ATC TAC CAC CTG CAG AAC CTT ACC ATC GAG GAC 1560
Gln Gly Leu Gln Ser Ile Tyr His Leu Gln Asn Leu Thr Ile Glu Asp
465 470 475

CTT GGG GCT CTG AAG GTC CCT GAC CAG TAC CGT ATG ACC ATC TGG AGG 1608
Leu Gly Ala Leu Lys Val Pro Asp Gln Tyr Arg Met Thr Ile Trp Arg
480 485 490 495

GGC CTA CAG GAC CTG AAG CAG AGC CAT GAC TGC GGC CAG CAA CTG CTA 1656
Gly Leu Gln Asp Leu Lys Gln Ser His Asp Cys Gly Gln Gln Leu Leu
500 505 510

CGC TCC AGC AGC AAC GCG GCC ACC ATC TCC ATC GGC GGC TCT GGC GAG 1704
Arg Ser Ser Ser Asn Ala Ala Thr Ile Ser Ile Gly Gly Ser Gly Glu
515 520 525

CTG CAG CGG CAG CGG GTC ATG GAA GCC GTG CAT TTC CGT GTG CGC CAC 1752
Leu Gln Arg Gln Arg Val Met Glu Ala Val His Phe Arg Val Arg His
530 535 540

ACC ATC ACA ATC CCC AAC CGT GGA GGC GCA GGT GCG GTG ACA GGT CCC 1800
Thr Ile Thr Ile Pro Asn Arg Gly Gly Ala Gly Ala Val Thr Gly Pro
545 550 555

GAC GAG TGG GCG GAC TTT GGC TTT GAC CTG CCT GAC TGC AAG TCC CGT 1848
Asp Glu Trp Ala Asp Phe Gly Phe Asp Leu Pro Asp Cys Lys Ser Arg
560 565 570 575

AAG CAG CCC ATC AAA GAG GAG TTC ACA GAG ACA GAG AGC CAC 1890
Lys Gln Pro Ile Lys Glu Glu Phe Thr Glu Thr Glu Ser His
580 585

TGAGGAACGT ACCTTCTTCT CCTGTCCTTC CTCTGTGAGA AACTGCTCTT GGAAGTGGGA 1950

CCTGTTGGCT GTGCCCACAG AAACCAGCAA GGACCTTCTG CCGGATGCCA TTCCTGAAGG 2010

GAAGTCGCTC ATGAACTAAC TCCCTCTTGG 2040

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 589 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Met Cys Met Gly Pro Val Tyr Glu Ser Leu Gly Gln Ala Gln Phe Asn
1 5 10 15

Leu Leu Ser Ser Ala Met Asp Gln Met Gly Ser Arg Ala Ala Pro Ala
20 25 30

Ser Pro Tyr Thr Pro Glu His Ala Ala Ser Ala Pro Thr His Ser Pro
35 40 45

Tyr Ala Gln Pro Ser Ser Thr Phe Asp Thr Met Ser Pro Ala Pro Val
50 55 60

Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His His Phe Glu Val Thr
65 70 75 80

Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Pro
85 90 95

Leu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln
100 105 110

Ile Lys Val Ser Thr Pro Pro Pro Pro Gly Thr Ala Ile Arg Ala Met
115 120 125

Pro Val Tyr Lys Lys Ala Glu His Val Thr Asp Ile Val Lys Arg Cys
130 135 140

Pro Asn His Glu Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser Ala Pro
145 150 155 160

Ala Ser His Leu Ile Arg Val Glu Gly Asn Asn Leu Ala Gln Tyr Val
165 170 175

Asp Asp Pro Val Thr Gly Arg Gln Ser Val Val Val Pro Tyr Glu Pro
180 185 190

Pro Gln Val Gly Thr Glu Phe Thr Thr Ile Leu Tyr Asn Phe Met Cys
195 200 205

Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Val Ile
210 215 220

Ile Thr Leu Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Ser Phe
225 230 235 240

Glu Gly Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu
245 250 255

Asp His Tyr Arg Glu Gln Gln Ala Leu Asn Glu Ser Thr Thr Lys Asn
260 265 270

Gly Ala Ala Ser Lys Arg Ala Phe Lys Gln Ser Pro Pro Ala Ile Pro
275 280 285

Ala Leu Gly Thr Asn Val Lys Lys Arg Arg His Gly Asp Glu Asp Met
290 295 300

Phe Tyr Met His Val Arg Gly Arg Glu Asn Phe Glu Ile Leu Met Lys
305 310 315 320

Val Lys Glu Ser Leu Glu Leu Met Glu Leu Val Pro Gln Pro Leu Val
325 330 335

Asp Ser Tyr Arg Gln Gln Gln Gln Gln Gln Leu Leu Gln Arg Pro Ser
340 345 350

His Leu Gln Pro Pro Ser Tyr Gly Pro Val Leu Ser Pro Met Asn Lys

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

```
Met Cys Met Gly Pro Val Tyr Glu Ser Leu Gly Gln Ala Gln Phe Asn
 1               5                  10                  15

Leu Leu Ser Ser Ala Met Asp Gln Met Gly Ser Arg Ala Ala Pro Ala
            20                  25                  30

Ser Pro Tyr Thr Pro Glu His Ala Ala Ser Ala Pro Thr His Ser Pro
        35                  40                  45

Tyr Ala Gln Pro Ser Ser Thr Phe Asp Thr Met Ser Pro Ala Pro Val
    50                  55                  60

Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His His Phe Glu Val Thr
65                  70                  75                  80

Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Pro
                85                  90                  95

Leu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln
            100                 105                 110

Ile Lys Val Ser Thr Pro Pro Pro Pro Gly Thr Ala Ile Arg Ala Met
        115                 120                 125

Pro Val Tyr Lys Lys Ala Glu His Val Thr Asp Ile Val Lys Arg Cys
    130                 135                 140

Pro Asn His Glu Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser Ala Pro
145                 150                 155                 160

Ala Ser His Leu Ile Arg Val Glu Gly Asn Asn Leu Ala Gln Tyr Val
                165                 170                 175

Asp Asp Pro Val Thr Gly Arg Gln Ser Val Val Val Pro Tyr Glu Pro
            180                 185                 190

Pro Gln Val Gly Thr Glu Phe Thr Thr Ile Leu Tyr Asn Phe Met Cys
        195                 200                 205

Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Val Ile
    210                 215                 220

Ile Thr Leu Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Ser Phe
225                 230                 235                 240

Glu Gly Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu
                245                 250                 255

Asp His Tyr Arg Glu Gln Gln Ala Leu Asn Glu Ser Thr Thr Lys Asn
            260                 265                 270

Gly Ala Ala Ser Lys Arg Ala Phe Lys Gln Ser Pro Pro Ala Ile Pro
        275                 280                 285

Ala Leu Gly Thr Asn Val Lys Lys Arg Arg His Gly Asp Glu Asp Met
    290                 295                 300

Phe Tyr Met His Val Arg Gly Arg Glu Asn Phe Glu Ile Leu Met Lys
305                 310                 315                 320

Val Lys Glu Ser Leu Glu Leu Met Glu Leu Val Pro Gln Pro Leu Val
                325                 330                 335

Asp Ser Tyr Arg Gln Gln Gln Gln Gln Gln Leu Leu Gln Arg Pro Ser
            340                 345                 350

His Leu Gln Pro Pro Ser Tyr Gly Pro Val Leu Ser Pro Met Asn Lys
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        355                 360                 365

Val His Gly Gly Val Asn Lys Leu Pro Ser Val Asn Gln Leu Val Gly
    370                 375                 380

Gln Pro Pro Pro His Ser Ser Ala Ala Gly Pro Asn Leu Gly Pro Met
385                 390                 395                 400

Gly Ser Gly Met Leu Asn Ser His Gly His Ser Met Pro Ala Asn Gly
                405                 410                 415

Glu Met Asn Gly Gly His Ser Ser Gln Thr Met Val Ser Gly Ser His
            420                 425                 430

Cys Thr Pro Pro Pro Pro Tyr His Ala Asp Pro Ser Leu Val Ser Phe
        435                 440                 445

Leu Thr Gly Leu Gly Cys Pro Asn Cys Ile Glu Cys Phe Thr Ser Gln
    450                 455                 460

Gly Leu Gln Ser Ile Tyr His Leu Gln Asn Leu Thr Ile Glu Asp Leu
465                 470                 475                 480

Gly Ala Leu Lys Val Pro Asp Gln Tyr Arg Met Thr Ile Trp Arg Gly
                485                 490                 495

Leu Gln Asp Leu Lys Gln Ser His Asp Cys Gly Gln Gln Leu Leu Arg
            500                 505                 510

Ser Ser Ser Asn Ala Ala Thr Ile Ser Ile Gly Gly Ser Gly Glu Leu
        515                 520                 525

Gln Arg Gln Arg Val Met Glu Ala Val His Phe Arg Val Arg His Thr
    530                 535                 540

Ile Thr Ile Pro Asn Arg Gly Gly Ala Gly Ala Val Thr Gly Pro Asp
545                 550                 555                 560

Glu Trp Ala Asp Phe Gly Phe Asp Leu Pro Asp Cys Lys Ser Arg Lys
                565                 570                 575

Gln Pro Ile Lys Glu Glu Phe Thr Glu Thr Glu Ser His
            580                 585
```

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 758 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Mus musculus

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 389..757

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

```
TGGTCCCGCT TCGACCAAGA CTCCGGCTAC CAGCTTGCGG GCCCCGCGGA GGAGGAGACC    60
CCGCTGGGGC TAGCTGGGCG ACGCGCGCCA AGCGGCGGCG GGAAGGAGGC GGGAGGAGCG   120
GGGCCCGAGA CCCCGACTCG GGCAGAGCCA GCTGGGGAGG CGGGGCGCGC GTGGGAGCCA   180
GGGGCCCGGG TGGCCGGCCC TCCTCCGCCA CGGCTGAGTG CCCGCGCTGC CTTCCCGCCG   240
```

GTCCGCCAAG AAAGGCGCTA AGCCTGCGGC AGTCCCCTCG CCGCCGCCTC CCTGCTCCGC 300

ACCCTTATAA CCCGCCGTCC CGCATCCAGG CGAGGAGGCA ACGCTGCAGC CCAGCCCTCG 360

CCGACGCCGA CGCCCGGCCC GGAGCAGA ATG AGC GGC AGC GTT GGG GAG ATG 412
Met Ser Gly Ser Val Gly Glu Met
1 5

GCC CAG ACC TCT TCT TCC TCC TCC TCC ACC TTC GAG CAC CTG TGG AGT 460
Ala Gln Thr Ser Ser Ser Ser Ser Ser Thr Phe Glu His Leu Trp Ser
10 15 20

TCT CTA GAG CCA GAC AGC ACC TAC TTT GAC CTC CCC CAG CCC AGC CAA 508
Ser Leu Glu Pro Asp Ser Thr Tyr Phe Asp Leu Pro Gln Pro Ser Gln
25 30 35 40

GGG ACT AGC GAG GCA TCA GGC AGC GAG GAG TCC AAC ATG GAT GTC TTC 556
Gly Thr Ser Glu Ala Ser Gly Ser Glu Glu Ser Asn Met Asp Val Phe
45 50 55

CAC CTG CAA GGC ATG GCC CAG TTC AAT TTG CTC AGC AGT GCC ATG GAC 604
His Leu Gln Gly Met Ala Gln Phe Asn Leu Leu Ser Ser Ala Met Asp
60 65 70

CAG ATG GGC AGC CGT GCG GCC CCG GCG AGC CCC TAC ACC CCG GAG CAC 652
Gln Met Gly Ser Arg Ala Ala Pro Ala Ser Pro Tyr Thr Pro Glu His
75 80 85

GCC GCC AGC GCG CCC ACC CAC TCG CCC TAC GCG CAG CCC AGC TCC ACC 700
Ala Ala Ser Ala Pro Thr His Ser Pro Tyr Ala Gln Pro Ser Ser Thr
90 95 100

TTC GAC ACC ATG TCT CCG GCG CCT GTC ATC CCT TCC AAT ACC GAC TAC 748
Phe Asp Thr Met Ser Pro Ala Pro Val Ile Pro Ser Asn Thr Asp Tyr
105 110 115 120

CCC GGC CCC C 758
Pro Gly Pro

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 123 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Met Ser Gly Ser Val Gly Glu Met Ala Gln Thr Ser Ser Ser Ser Ser
1 5 10 15

Ser Thr Phe Glu His Leu Trp Ser Ser Leu Glu Pro Asp Ser Thr Tyr
20 25 30

Phe Asp Leu Pro Gln Pro Ser Gln Gly Thr Ser Glu Ala Ser Gly Ser
35 40 45

Glu Glu Ser Asn Met Asp Val Phe His Leu Gln Gly Met Ala Gln Phe
50 55 60

Asn Leu Leu Ser Ser Ala Met Asp Gln Met Gly Ser Arg Ala Ala Pro
65 70 75 80

Ala Ser Pro Tyr Thr Pro Glu His Ala Ala Ser Ala Pro Thr His Ser
85 90 95

Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Thr Met Ser Pro Ala Pro
100 105 110

Val Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro
115 120

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 559 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

CGACCTTCCC CAGTCAAGCC GGGGGAATAA TGAGGTGGTG GGCGGAACGG ATTCCAGCAT 60

GGACGTCTTC CACCTGGAGG GCATGACTAC ATCTGTCATG CATCCTCGGC TCCTGCCTCA 120

CTAGCTGCGG AGCCTCTCCC GCTCGGTCCA CGCTGCCGGG CGGCCACGAC CGTGACCCTT 180

CCCCTCGGGC CGCCCAGATC CATGCCTCGT CCCACGGGAC ACCAGTTCCC TGGCGTGTGC 240

AGACCCCCCG GCGCCTACCA TGCTGTACGT CGGTGACCCC GCACGGCACC TCGCCACGGC 300

CCAGTTCAAT CTGCTGAGCA GCACCATGGA CCAGATGAGC AGCCGCGCGG CCTCGGCCAG 360

CCCCTACACC CCAGAGCACG CCGCCAGCGT GCCCACCCAC TCGCCCTACG CACAACCCAG 420

CTCCACCTTC GACACCATGT CGCCGGCGCC TGTCATCCCC TCCAACACCG ACTACCCCGG 480

ACCCCACCAC TTTGAGGTCA CTTTCCAGCA GTCCAGCACG GCCAAGTCAG CCACCTGGAC 540

GTACTCCCCG CTCTTGAAG 559

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1764 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

ATGCTGTACG TCGGTGACCC CGCACGGCAC CTCGCCACGG CCCAGTTCAA TCTGCTGAGC 60

AGCACCATGG ACCAGATGAG CAGCCGCGCG GCCTCGGCCA GCCCCTACAC CCCAGAGCAC 120

GCCGCCAGCG TGCCCACCCA CTCGCCCTAC GCACAACCCA GCTCCACCTT CGACACCATG 180

TCGCCGGCGC CTGTCATCCC CTCCAACACC GACTACCCCG GACCCCACCA CTTTGAGGTC 240

ACTTTCCAGC AGTCCAGCAC GGCCAAGTCA GCCACCTGGA CGTACTCCCC GCTCTTGAAG 300

AAACTCTACT GCCAGATCGC CAAGACATGC CCCATCCAGA TCAAGGTGTC CACCCCGCCA 360

CCCCCAGGCA CTGCCATCCG GGCCATGCCT GTTTACAAGA AAGCGGAGCA CGTGACCGAC 420

GTCGTGAAAC GCTGCCCCAA CCACGAGCTC GGGAGGGACT TCAACGAAGG ACAGTCTGCT 480

CCAGCCAGCC ACCTCATCCG CGTGGAAGGC AATAATCTCT CGCAGTATGT GGATGACCCT 540

GTCACCGGCA GGCAGAGCGT CGTGGTGCCC TATGAGCCAC CACAGGTGGG GACGGAATTC 600

ACCACCATCC TGTACAACTT CATGTGTAAC AGCAGCTGTG TAGGGGGCAT GAACCGGCGG 660

CCCATCCTCA TCATCATCAC CCTGGAGATG CGGGATGGGC AGGTGCTGGG CCGCCGGTCC 720

TTTGAGGGCC GCATCTGCGC CTGTCCTGGC CGCGACCGAA AAGCTGATGA GGACCACTAC 780

CGGGAGCAGC AGGCCCTGAA CGAGAGCTCC GCCAAGAACG GGGCCGCCAG CAAGCGTGCC 840

TTCAAGCAGA GCCCCCCTGC CGTCCCCGCC CTTGGTGCCG GTGTGAAGAA GCGGCGGCAT 900

GGAGACGAGG ACACGTACTA CCTTCAGGTG CGAGGCCGGG AGAACTTTGA GATCCTGATG 960

AAGCTGAAAG AGAGCCTGGA GCTGATGGAG TTGGTGCCGC AGCCACTGGT GGACTCCTAT 1020

CGGCAGCAGC AGCAGCTCCT ACAGAGGCCG AGTCACCTAC AGCCCCCGTC CTACGGGCCG 1080

GTCCTCTCGC CCATGAACAA GGTGCACGGG GGCATGAACA AGCTGCCCTC CGTCAACCAG 1140

CTGGTGGGCC AGCCTCCCCC GCACAGTTCG GCAGCTACAC CCAACCTGGG GCCCGTGGGC 1200

CCCGGGATGC TCAACAACCA TGGCCACGCA GTGCCAGCCA ACGGCGAGAT GAGCAGCAGC 1260

CACAGCGCCC AGTCCATGGT CTCGGGGTCC CACTGCACTC CGCCACCCCC CTACCACGCC 1320

GACCCCAGCC TCGTCAGTTT TTTAACAGGA TTGGGGTGTC CAAACTGCAT CGAGTATTTC 1380

ACCTCCCAAG GGTTACAGAG CATTTACCAC CTGCAGAACC TGACCATTGA GGACCTGGGG 1440

GCCCTGAAGA TCCCCGAGCA GTACCGCATG ACCATCTGGC GGGGCCTGCA GGACCTGAAG 1500

CAGGGCCACG ACTACAGCAC CGCGCAGCAG CTGCTCCGCT CTAGCAACGC GGCCACCATC 1560

TCCATCGGCG GCTCAGGGGA ACTGCAGCGC CAGCGGGTCA TGGAGGCCGT GCACTTCCGC 1620

GTGCGCCACA CCATCACCAT CCCCAACCGC GGCGGCCCAG GCGGCGGCCC TGACGAGTGG 1680

GCGGACTTCG GCTTCGACCT GCCCGACTGC AAGGCCCGCA AGCAGCCCAT CAAGGAGGAG 1740

TTCACGGAGG CCGAGATCCA CTGA 1764

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 587 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Met Leu Tyr Val Gly Asp Pro Ala Arg His Leu Ala Thr Ala Gln Phe
1 5 10 15

Asn Leu Leu Ser Ser Thr Met Asp Gln Met Ser Ser Arg Ala Ala Ser
20 25 30

Ala Ser Pro Tyr Thr Pro Glu His Ala Ala Ser Val Pro Thr His Ser
35 40 45

Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Thr Met Ser Pro Ala Pro
50 55 60

Val Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His His Phe Glu Val
65 70 75 80

```
Thr Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser
                85                  90                  95

Pro Leu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile
            100                 105                 110

Gln Ile Lys Val Ser Thr Pro Pro Pro Pro Gly Thr Ala Ile Arg Ala
        115                 120                 125

Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Asp Val Val Lys Arg
    130                 135                 140

Cys Pro Asn His Glu Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser Ala
145                 150                 155                 160

Pro Ala Ser His Leu Ile Arg Val Glu Gly Asn Asn Leu Ser Gln Tyr
                165                 170                 175

Val Asp Asp Pro Val Thr Gly Arg Gln Ser Val Val Val Pro Tyr Glu
            180                 185                 190

Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Ile Leu Tyr Asn Phe Met
        195                 200                 205

Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile
    210                 215                 220

Ile Ile Thr Leu Glu Met Arg Asp Gly Gln Val Leu Gly Arg Arg Ser
225                 230                 235                 240

Phe Glu Gly Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp
                245                 250                 255

Glu Asp His Tyr Arg Glu Gln Gln Ala Leu Asn Glu Ser Ser Ala Lys
            260                 265                 270

Asn Gly Ala Ala Ser Lys Arg Ala Phe Lys Gln Ser Pro Pro Ala Val
        275                 280                 285

Pro Ala Leu Gly Ala Gly Val Lys Lys Arg Arg His Gly Asp Glu Asp
    290                 295                 300

Thr Tyr Tyr Leu Gln Val Arg Gly Arg Glu Asn Phe Glu Ile Leu Met
305                 310                 315                 320

Lys Leu Lys Glu Ser Leu Glu Leu Met Glu Leu Val Pro Gln Pro Leu
                325                 330                 335

Val Asp Ser Tyr Arg Gln Gln Gln Gln Leu Leu Gln Arg Pro Ser His
            340                 345                 350

Leu Gln Pro Pro Ser Tyr Gly Pro Val Leu Ser Pro Met Asn Lys Val
        355                 360                 365

His Gly Gly Met Asn Lys Leu Pro Ser Val Asn Gln Leu Val Gly Gln
    370                 375                 380

Pro Pro Pro His Ser Ser Ala Ala Thr Pro Asn Leu Gly Pro Val Gly
385                 390                 395                 400

Pro Gly Met Leu Asn Asn His Gly His Ala Val Pro Ala Asn Gly Glu
                405                 410                 415

Met Ser Ser Ser His Ser Ala Gln Ser Met Val Ser Gly Ser His Cys
            420                 425                 430

Thr Pro Pro Pro Pro Tyr His Ala Asp Pro Ser Leu Val Ser Phe Leu
        435                 440                 445

Thr Gly Leu Gly Cys Pro Asn Cys Ile Glu Tyr Phe Thr Ser Gln Gly
    450                 455                 460
```

```
Leu Gln Ser Ile Tyr His Leu Gln Asn Leu Thr Ile Glu Asp Leu Gly
465                 470                 475                 480

Ala Leu Lys Ile Pro Glu Gln Tyr Arg Met Thr Ile Trp Arg Gly Leu
                485                 490                 495

Gln Asp Leu Lys Gln Gly His Asp Tyr Ser Thr Ala Gln Gln Leu Leu
            500                 505                 510

Arg Ser Ser Asn Ala Ala Thr Ile Ser Ile Gly Gly Ser Gly Glu Leu
        515                 520                 525

Gln Arg Gln Arg Val Met Glu Ala Val His Phe Arg Val Arg His Thr
    530                 535                 540

Ile Thr Ile Pro Asn Arg Gly Gly Pro Gly Gly Gly Pro Asp Glu Trp
545                 550                 555                 560

Ala Asp Phe Gly Phe Asp Leu Pro Asp Cys Lys Ala Arg Lys Gln Pro
                565                 570                 575

Ile Lys Glu Glu Phe Thr Glu Ala Glu Ile His
            580                 585
```

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1521 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

```
ATGCTGTACG TCGGTGACCC CGCACGGCAC CTCGCCACGG CCCAGTTCAA TCTGCTGAGC      60
AGCACCATGG ACCAGATGAG CAGCCGCGCG GCCTCGGCCA GCCCCTACAC CCCAGAGCAC     120
GCCGCCAGCG TGCCCACCCA CTCGCCCTAC GCACAACCCA GCTCCACCTT CGACACCATG     180
TCGCCGGCGC CTGTCATCCC CTCCAACACC GACTACCCCG GACCCCACCA CTTTGAGGTC     240
ACTTTCCAGC AGTCCAGCAC GGCCAAGTCA GCCACCTGGA CGTACTCCCC GCTCTTGAAG     300
AAACTCTACT GCCAGATCGC CAAGACATGC CCCATCCAGA TCAAGGTGTC CACCCCGCCA     360
CCCCCAGGCA CTGCCATCCG GGCCATGCCT GTTTACAAGA AAGCGGAGCA CGTGACCGAC     420
GTCGTGAAAC GCTGCCCCAA CCACGAGCTC GGGAGGGACT TCAACGAAGG ACAGTCTGCT     480
CCAGCCAGCC ACCTCATCCG CGTGGAAGGC AATAATCTCT CGCAGTATGT GGATGACCCT     540
GTCACCGGCA GGCAGAGCGT CGTGGTGCCC TATGAGCCAC CACAGGTGGG GACGGAATTC     600
ACCACCATCC TGTACAACTT CATGTGTAAC AGCAGCTGTG TAGGGGGCAT GAACCGGCGG     660
CCCATCCTCA TCATCATCAC CCTGGAGATG CGGGATGGGC AGGTGCTGGG CCGCCGGTCC     720
TTTGAGGGCC GCATCTGCGC CTGTCCTGGC CGCGACCGAA AAGCTGATGA GGACCACTAC     780
CGGGAGCAGC AGGCCCTGAA CGAGAGCTCC GCCAAGAACG GGGCCGCCAG CAAGCGTGCC     840
TTCAAGCAGA GCCCCCCTGC CGTCCCCGCC CTTGGTGCCG GTGTGAAGAA GCGGCGGCAT     900
GGAGACGAGG ACACGTACTA CCTTCAGGTG CGAGGCCGGG AGAACTTTGA GATCCTGATG     960
```

AAGCTGAAAG AGAGCCTGGA GCTGATGGAG TTGGTGCCGC AGCCACTGGT GGACTCCTAT 1020

CGGCAGCAGC AGCAGCTCCT ACAGAGGCCG CCCCGGGATG CTCAACAACC ATGGCCACGC 1080

AGTGCCAGCC AACGGCGAGA TGAGCAGCAG CCACAGCGCC CAGTCCATGG TCTCGGGGTC 1140

CCACTGCACT CCGCCACCCC CCTACCACGC CGACCCCAGC CTCGTCAGGA CCTGGGGGCC 1200

CTGAAGATCC CCGAGCAGTA CCGCATGACC ATCTGGCGGG GCCTGCAGGA CCTGAAGCAG 1260

GGCCACGACT ACAGCACCGC GCAGCAGCTG CTCCGCTCTA GCAACGCGGC CACCATCTCC 1320

ATCGGCGGCT CAGGGGAACT GCAGCGCCAG CGGGTCATGG AGGCCGTGCA CTTCCGCGTG 1380

CGCCACACCA TCACCATCCC CAACCGCGGC GGCCCAGGCG GCGGCCCTGA CGAGTGGGCG 1440

GACTTCGGCT TCGACCTGCC CGACTGCAAG GCCCGCAAGC AGCCCATCAA GGAGGAGTTC 1500

ACGGAGGCCG AGATCCACTG A 1521

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 506 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Met Leu Tyr Val Gly Asp Pro Ala Arg His Leu Ala Thr Ala Gln Phe
1 5 10 15

Asn Leu Leu Ser Ser Thr Met Asp Gln Met Ser Ser Arg Ala Ala Ser
20 25 30

Ala Ser Pro Tyr Thr Pro Glu His Ala Ala Ser Val Pro Thr His Ser
35 40 45

Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Thr Met Ser Pro Ala Pro
50 55 60

Val Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His His Phe Glu Val
65 70 75 80

Thr Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser
85 90 95

Pro Leu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile
100 105 110

Gln Ile Lys Val Ser Thr Pro Pro Pro Pro Gly Thr Ala Ile Arg Ala
115 120 125

Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Asp Val Val Lys Arg
130 135 140

Cys Pro Asn His Glu Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser Ala
145 150 155 160

Pro Ala Ser His Leu Ile Arg Val Glu Gly Asn Asn Leu Ser Gln Tyr
165 170 175

Val Asp Asp Pro Val Thr Gly Arg Gln Ser Val Val Val Pro Tyr Glu
180 185 190

Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Ile Leu Tyr Asn Phe Met
195 200 205

Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile
    210   215   220

Ile Ile Thr Leu Glu Met Arg Asp Gly Gln Val Leu Gly Arg Arg Ser
225   230   235   240

Phe Glu Gly Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp
                245   250   255

Glu Asp His Tyr Arg Glu Gln Gln Ala Leu Asn Glu Ser Ser Ala Lys
            260   265   270

Asn Gly Ala Ala Ser Lys Arg Ala Phe Lys Gln Ser Pro Pro Ala Val
        275   280   285

Pro Ala Leu Gly Ala Gly Val Lys Lys Arg Arg His Gly Asp Glu Asp
    290   295   300

Thr Tyr Tyr Leu Gln Val Arg Gly Arg Glu Asn Phe Glu Ile Leu Met
305   310   315   320

Lys Leu Lys Glu Ser Leu Glu Leu Met Glu Leu Val Pro Gln Pro Leu
                325   330   335

Val Asp Ser Tyr Arg Gln Gln Gln Gln Leu Leu Gln Arg Pro Pro Arg
            340   345   350

Asp Ala Gln Gln Pro Trp Pro Arg Ser Ala Ser Gln Arg Arg Asp Glu
        355   360   365

Gln Gln Pro Gln Arg Pro Val His Gly Leu Gly Val Pro Leu His Ser
    370   375   380

Ala Thr Pro Leu Pro Arg Arg Pro Gln Pro Arg Gln Asp Leu Gly Ala
385   390   395   400

Leu Lys Ile Pro Glu Gln Tyr Arg Met Thr Ile Trp Arg Gly Leu Gln
                405   410   415

Asp Leu Lys Gln Gly His Asp Tyr Ser Thr Ala Gln Gln Leu Leu Arg
            420   425   430

Ser Ser Asn Ala Ala Thr Ile Ser Ile Gly Gly Ser Gly Glu Leu Gln
        435   440   445

Arg Gln Arg Val Met Glu Ala Val His Phe Arg Val Arg His Thr Ile
    450   455   460

Thr Ile Pro Asn Arg Gly Gly Pro Gly Gly Gly Pro Asp Glu Trp Ala
465   470   475   480

Asp Phe Gly Phe Asp Leu Pro Asp Cys Lys Ala Arg Lys Gln Pro Ile
                485   490   495

Lys Glu Glu Phe Thr Glu Ala Glu Ile His
            500   505

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1870 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(ix) FEATURE:
(A) NAME/KEY: CDS

(B) LOCATION: 104..1867

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

```
TGCCCGGGGC TGCGACGGCT GCAGGGAACC AGACAGCACC TACTTCGACC TTCCCCAGTC       60

AAGCCGGGGG AATAATGAGG TGGTGGGCGG AACGGATTCC AGC ATG GAC GTC TTC        115
                                                Met Asp Val Phe
                                                  1

CAC CTG GAG GGC ATG ACT ACA TCT GTC ATG GCC CAG TTC AAT CTG CTG        163
His Leu Glu Gly Met Thr Thr Ser Val Met Ala Gln Phe Asn Leu Leu
  5                  10                  15                  20

AGC AGC ACC ATG GAC CAG ATG AGC AGC CGC GCG GCC TCG GCC AGC CCC        211
Ser Ser Thr Met Asp Gln Met Ser Ser Arg Ala Ala Ser Ala Ser Pro
                 25                  30                  35

TAC ACC CCA GAG CAC GCC GCC AGC GTG CCC ACC CAC TCG CCC TAC GCA        259
Tyr Thr Pro Glu His Ala Ala Ser Val Pro Thr His Ser Pro Tyr Ala
             40                  45                  50

CAA CCC AGC TCC ACC TTC GAC ACC ATG TCG CCG GCG CCT GTC ATC CCC        307
Gln Pro Ser Ser Thr Phe Asp Thr Met Ser Pro Ala Pro Val Ile Pro
         55                  60                  65

TCC AAC ACC GAC TAC CCC GGA CCC CAC CAC TTT GAG GTC ACT TTC CAG        355
Ser Asn Thr Asp Tyr Pro Gly Pro His His Phe Glu Val Thr Phe Gln
     70                  75                  80

CAG TCC AGC ACG GCC AAG TCA GCC ACC TGG ACG TAC TCC CCG CTC TTG        403
Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Pro Leu Leu
 85                  90                  95                 100

AAG AAA CTC TAC TGC CAG ATC GCC AAG ACA TGC CCC ATC CAG ATC AAG        451
Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys
                105                 110                 115

GTG TCC ACC CCG CCA CCC CCA GGC ACT GCC ATC CGG GCC ATG CCT GTT        499
Val Ser Thr Pro Pro Pro Pro Gly Thr Ala Ile Arg Ala Met Pro Val
            120                 125                 130

TAC AAG AAA GCG GAG CAC GTG ACC GAC GTC GTG AAA CGC TGC CCC AAC        547
Tyr Lys Lys Ala Glu His Val Thr Asp Val Val Lys Arg Cys Pro Asn
        135                 140                 145

CAC GAG CTC GGG AGG GAC TTC AAC GAA GGA CAG TCT GCT CCA GCC AGC        595
His Glu Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser Ala Pro Ala Ser
    150                 155                 160

CAC CTC ATC CGC GTG GAA GGC AAT AAT CTC TCG CAG TAT GTG GAT GAC        643
His Leu Ile Arg Val Glu Gly Asn Asn Leu Ser Gln Tyr Val Asp Asp
165                 170                 175                 180

CCT GTC ACC GGC AGG CAG AGC GTC GTG GTG CCC TAT GAG CCA CCA CAG        691
Pro Val Thr Gly Arg Gln Ser Val Val Val Pro Tyr Glu Pro Pro Gln
                185                 190                 195

GTG GGG ACG GAA TTC ACC ACC ATC CTG TAC AAC TTC ATG TGT AAC AGC        739
Val Gly Thr Glu Phe Thr Thr Ile Leu Tyr Asn Phe Met Cys Asn Ser
            200                 205                 210

AGC TGT GTA GGG GGC ATG AAC CGG CGG CCC ATC CTC ATC ATC ATC ACC        787
Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Ile Thr
        215                 220                 225

CTG GAG ATG CGG GAT GGG CAG GTG CTG GGC CGC CGG TCC TTT GAG GGC        835
Leu Glu Met Arg Asp Gly Gln Val Leu Gly Arg Arg Ser Phe Glu Gly
    230                 235                 240

CGC ATC TGC GCC TGT CCT GGC CGC GAC CGA AAA GCT GAT GAG GAC CAC        883
```

Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp His
245 250 255 260

TAC CGG GAG CAG CAG GCC CTG AAC GAG AGC TCC GCC AAG AAC GGG GCC 931
Tyr Arg Glu Gln Gln Ala Leu Asn Glu Ser Ser Ala Lys Asn Gly Ala
265 270 275

GCC AGC AAG CGT GCC TTC AAG CAG AGC CCC CCT GCC GTC CCC GCC CTT 979
Ala Ser Lys Arg Ala Phe Lys Gln Ser Pro Pro Ala Val Pro Ala Leu
280 285 290

GGT GCC GGT GTG AAG AAG CGG CGG CAT GGA GAC GAG GAC ACG TAC TAC 1027
Gly Ala Gly Val Lys Lys Arg Arg His Gly Asp Glu Asp Thr Tyr Tyr
295 300 305

CTT CAG GTG CGA GGC CGG GAG AAC TTT GAG ATC CTG ATG AAG CTG AAA 1075
Leu Gln Val Arg Gly Arg Glu Asn Phe Glu Ile Leu Met Lys Leu Lys
310 315 320

GAG AGC CTG GAG CTG ATG GAG TTG GTG CCG CAG CCA CTG GTG GAC TCC 1123
Glu Ser Leu Glu Leu Met Glu Leu Val Pro Gln Pro Leu Val Asp Ser
325 330 335 340

TAT CGG CAG CAG CAG CAG CTC CTA CAG AGG CCG AGT CAC CTA CAG CCC 1171
Tyr Arg Gln Gln Gln Gln Leu Leu Gln Arg Pro Ser His Leu Gln Pro
345 350 355

CCG TCC TAC GGG CCG GTC CTC TCG CCC ATG AAC AAG GTG CAC GGG GGC 1219
Pro Ser Tyr Gly Pro Val Leu Ser Pro Met Asn Lys Val His Gly Gly
360 365 370

ATG AAC AAG CTG CCC TCC GTC AAC CAG CTG GTG GGC CAG CCT CCC CCG 1267
Met Asn Lys Leu Pro Ser Val Asn Gln Leu Val Gly Gln Pro Pro Pro
375 380 385

CAC AGT TCG GCA GCT ACA CCC AAC CTG GGG CCC GTG GGC CCC GGG ATG 1315
His Ser Ser Ala Ala Thr Pro Asn Leu Gly Pro Val Gly Pro Gly Met
390 395 400

CTC AAC AAC CAT GGC CAC GCA GTG CCA GCC AAC GGC GAG ATG AGC AGC 1363
Leu Asn Asn His Gly His Ala Val Pro Ala Asn Gly Glu Met Ser Ser
405 410 415 420

AGC CAC AGC GCC CAG TCC ATG GTC TCG GGG TCC CAC TGC ACT CCG CCA 1411
Ser His Ser Ala Gln Ser Met Val Ser Gly Ser His Cys Thr Pro Pro
425 430 435

CCC CCC TAC CAC GCC GAC CCC AGC CTC GTC AGT TTT TTA ACA GGA TTG 1459
Pro Pro Tyr His Ala Asp Pro Ser Leu Val Ser Phe Leu Thr Gly Leu
440 445 450

GGG TGT CCA AAC TGC ATC GAG TAT TTC ACC TCC CAA GGG TTA CAG AGC 1507
Gly Cys Pro Asn Cys Ile Glu Tyr Phe Thr Ser Gln Gly Leu Gln Ser
455 460 465

ATT TAC CAC CTG CAG AAC CTG ACC ATT GAG GAC CTG GGG GCC CTG AAG 1555
Ile Tyr His Leu Gln Asn Leu Thr Ile Glu Asp Leu Gly Ala Leu Lys
470 475 480

ATC CCC GAG CAG TAC CGC ATG ACC ATC TGG CGG GGC CTG CAG GAC CTG 1603
Ile Pro Glu Gln Tyr Arg Met Thr Ile Trp Arg Gly Leu Gln Asp Leu
485 490 495 500

AAG CAG GGC CAC GAC TAC AGC ACC GCG CAG CAG CTG CTC CGC TCT AGC 1651
Lys Gln Gly His Asp Tyr Ser Thr Ala Gln Gln Leu Leu Arg Ser Ser
505 510 515

AAC GCG GCC ACC ATC TCC ATC GGC GGC TCA GGG GAA CTG CAG CGC CAG 1699
Asn Ala Ala Thr Ile Ser Ile Gly Gly Ser Gly Glu Leu Gln Arg Gln
520 525 530

CGG GTC ATG GAG GCC GTG CAC TTC CGC GTG CGC CAC ACC ATC ACC ATC 1747

Arg Val Met Glu Ala Val His Phe Arg Val Arg His Thr Ile Thr Ile
535 540 545

CCC AAC CGC GGC GGC CCA GGC GGC GGC CCT GAC GAG TGG GCG GAC TTC 1795
Pro Asn Arg Gly Gly Pro Gly Gly Gly Pro Asp Glu Trp Ala Asp Phe
550 555 560

GGC TTC GAC CTG CCC GAC TGC AAG GCC CGC AAG CAG CCC ATC AAG GAG 1843
Gly Phe Asp Leu Pro Asp Cys Lys Ala Arg Lys Gln Pro Ile Lys Glu
565 570 575 580

GAG TTC ACG GAG GCC GAG ATC CAC TGA 1870
Glu Phe Thr Glu Ala Glu Ile His
585

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 588 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

Met Asp Val Phe His Leu Glu Gly Met Thr Thr Ser Val Met Ala Gln
1 5 10 15

Phe Asn Leu Leu Ser Ser Thr Met Asp Gln Met Ser Ser Arg Ala Ala
20 25 30

Ser Ala Ser Pro Tyr Thr Pro Glu His Ala Ala Ser Val Pro Thr His
35 40 45

Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Thr Met Ser Pro Ala
50 55 60

Pro Val Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His His Phe Glu
65 70 75 80

Val Thr Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr
85 90 95

Ser Pro Leu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro
100 105 110

Ile Gln Ile Lys Val Ser Thr Pro Pro Pro Pro Gly Thr Ala Ile Arg
115 120 125

Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Asp Val Val Lys
130 135 140

Arg Cys Pro Asn His Glu Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser
145 150 155 160

Ala Pro Ala Ser His Leu Ile Arg Val Glu Gly Asn Asn Leu Ser Gln
165 170 175

Tyr Val Asp Asp Pro Val Thr Gly Arg Gln Ser Val Val Val Pro Tyr
180 185 190

Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Ile Leu Tyr Asn Phe
195 200 205

Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu
210 215 220

Ile Ile Ile Thr Leu Glu Met Arg Asp Gly Gln Val Leu Gly Arg Arg
225 230 235 240

Ser Phe Glu Gly Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala
245 250 255

Asp Glu Asp His Tyr Arg Glu Gln Gln Ala Leu Asn Glu Ser Ser Ala
260 265 270

Lys Asn Gly Ala Ala Ser Lys Arg Ala Phe Lys Gln Ser Pro Pro Ala
275 280 285

Val Pro Ala Leu Gly Ala Gly Val Lys Lys Arg Arg His Gly Asp Glu
290 295 300

Asp Thr Tyr Tyr Leu Gln Val Arg Gly Arg Glu Asn Phe Glu Ile Leu
305 310 315 320

Met Lys Leu Lys Glu Ser Leu Glu Leu Met Glu Leu Val Pro Gln Pro
325 330 335

Leu Val Asp Ser Tyr Arg Gln Gln Gln Gln Leu Leu Gln Arg Pro Ser
340 345 350

His Leu Gln Pro Pro Ser Tyr Gly Pro Val Leu Ser Pro Met Asn Lys
355 360 365

Val His Gly Gly Met Asn Lys Leu Pro Ser Val Asn Gln Leu Val Gly
370 375 380

Gln Pro Pro Pro His Ser Ser Ala Ala Thr Pro Asn Leu Gly Pro Val
385 390 395 400

Gly Pro Gly Met Leu Asn Asn His Gly His Ala Val Pro Ala Asn Gly
405 410 415

Glu Met Ser Ser Ser His Ser Ala Gln Ser Met Val Ser Gly Ser His
420 425 430

Cys Thr Pro Pro Pro Pro Tyr His Ala Asp Pro Ser Leu Val Ser Phe
435 440 445

Leu Thr Gly Leu Gly Cys Pro Asn Cys Ile Glu Tyr Phe Thr Ser Gln
450 455 460

Gly Leu Gln Ser Ile Tyr His Leu Gln Asn Leu Thr Ile Glu Asp Leu
465 470 475 480

Gly Ala Leu Lys Ile Pro Glu Gln Tyr Arg Met Thr Ile Trp Arg Gly
485 490 495

Leu Gln Asp Leu Lys Gln Gly His Asp Tyr Ser Thr Ala Gln Gln Leu
500 505 510

Leu Arg Ser Ser Asn Ala Ala Thr Ile Ser Ile Gly Gly Ser Gly Glu
515 520 525

Leu Gln Arg Gln Arg Val Met Glu Ala Val His Phe Arg Val Arg His
530 535 540

Thr Ile Thr Ile Pro Asn Arg Gly Gly Pro Gly Gly Gly Pro Asp Glu
545 550 555 560

Trp Ala Asp Phe Gly Phe Asp Leu Pro Asp Cys Lys Ala Arg Lys Gln
565 570 575

Pro Ile Lys Glu Glu Phe Thr Glu Ala Glu Ile His
580 585

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1817 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

```
ATGGCCCAGT CCACCGCCAC CTCCCCTGAT GGGGGCACCA CGTTTGAGCA CCTCTGGAGC      60
TCTCTGGAAC CAGACAGCAC CTACTTCGAC CTTCCCCAGT CAAGCCGGGG GAATAATGAG     120
GTGGTGGGCG GAACGGATTC CAGCATGGAC GTCTTCCACC TGGAGGGCAT GACTACATCT     180
GTCATGGCCC AGTTCAATCT GCTGAGCAGC ACCATGGACC AGATGAGCAG CCGCGCGGCC     240
TCGGCCAGCC CCTACACCCC AGAGCACGCC GCCAGCGTGC CCACCCACTC GCCCTACGCA     300
CAACCCAGCT CCACCTTCGA CACCATGTCG CCGGCGCCTG TCATCCCCTC CAACACCGAC     360
TACCCCGGAC CCCACCACTT TGAGGTCACT TTCCAGCAGT CCAGCACGGC CAAGTCAGCC     420
ACCTGGACGT ACTCCCCGCT CTTGAAGAAA CTCTACTGCC AGATCGCCAA GACATGCCCC     480
ATCCAGATCA AGGTGTCCAC CCCGCCACCC CCAGGCACTG CCATCCGGGC CATGCCTGTT     540
TACAAGAAAG CGGAGCACGT GACCGACGTC GTGAAACGCT GCCCCAACCA CGAGCTCGGG     600
AGGGACTTCA ACGAAGGACA GTCTGCTCCA GCCAGCCACC TCATCCGCGT GGAAGGCAAT     660
AATCTCTCGC AGTATGTGGA TGACCCTGTC ACCGGCAGGC AGAGCGTCGT GGTGCCCTAT     720
GAGCCACCAC AGGTGGGGAC GGAATTCACC ACCATCCTGT ACAACTTCAT GTGTAACAGC     780
AGCTGTGTAG GGGGCATGAA CCGGCGGCCC ATCCTCATCA TCATCACCCT GGAGATGCGG     840
GATGGGCAGG TGCTGGGCCG CCGGTCCTTT GAGGGCCGCA TCTGCGCCTG TCCTGGCCGC     900
GACCGAAAAG CTGATGAGGA CCACTACCGG GAGCAGCAGG CCCTGAACGA GAGCTCCGCC     960
AAGAACGGGG CCGCCAGCAA GCGTGCCTTC AAGCAGAGCC CCCCTGCCGT CCCCGCCCTT    1020
GGTGCCGGTG TGAAGAAGCG GCGGCATGGA GACGAGGACA CGTACTACCT TCAGGTGCGA    1080
GGCCGGGAGA ACTTTGAGAT CCTGATGAAG CTGAAAGAGA GCCTGGAGCT GATGGAGTTG    1140
GTGCCGCAGC CACTGGTGGA CTCCTATCGG CAGCAGCAGC AGCTCCTACA GAGGCCGAGT    1200
CACCTACAGC CCCCGTCCTA CGGGCCGGTC CTCTCGCCCA TGAACAAGGT GCACGGGGGC    1260
ATGAACAAGC TGCCCTCCGT CAACCAGCTG GTGGGCCAGC CTCCCCCGCA CAGTTCGGCA    1320
GCTACACCCA ACCTGGGGCC CGTGGGCCCC GGGATGCTCA ACAACCATGG CCACGCAGTG    1380
CCAGCCAACG GCGAGATGAG CAGCAGCCAC AGCGCCCAGT CCATGGTCTC GGGGTCCCAC    1440
TGCACTCCGC CACCCCCCTA CCACGCCGAC CCCAGCCTCG TCAGGACCTG GGGGCCCTGA    1500
AGATCCCCGA GCAGTACCGC ATGACCATCT GGCGGGGCCT GCAGGACCTG AAGCAGGGCC    1560
ACGACTACAG CACCGCGCAG CAGCTGCTCC GCTCTAGCAA CGCGGCCACC ATCTCCATCG    1620
GCGGCTCAGG GGAACTGCAG CGCCAGCGGG TCATGGAGGC CGTGCACTTC CGCGTGCGCC    1680
ACACCATCAC CATCCCCAAC CGCGGCGGCC CAGGCGGCGG CCCTGACGAG TGGGCGGACT    1740
TCGGCTTCGA CCTGCCCGAC TGCAAGGCCC GCAAGCAGCC CATCAAGGAG GAGTTCACGG    1800
AGGCCGAGAT CCACTGA                                                  1817
```

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 499 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

```
Met Ala Gln Ser Thr Ala Thr Ser Pro Asp Gly Gly Thr Thr Phe Glu
1               5                   10                  15

His Leu Trp Ser Ser Leu Glu Pro Asp Ser Thr Tyr Phe Asp Leu Pro
            20                  25                  30

Gln Ser Ser Arg Gly Asn Asn Glu Val Val Gly Gly Thr Asp Ser Ser
        35                  40                  45

Met Asp Val Phe His Leu Glu Gly Met Thr Thr Ser Val Met Ala Gln
    50                  55                  60

Phe Asn Leu Leu Ser Ser Thr Met Asp Gln Met Ser Ser Arg Ala Ala
65                  70                  75                  80

Ser Ala Ser Pro Tyr Thr Pro Glu His Ala Ala Ser Val Pro Thr His
                85                  90                  95

Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Thr Met Ser Pro Ala
            100                 105                 110

Pro Val Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His His Phe Glu
        115                 120                 125

Val Thr Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr
    130                 135                 140

Ser Pro Leu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro
145                 150                 155                 160

Ile Gln Ile Lys Val Ser Thr Pro Pro Pro Pro Gly Thr Ala Ile Arg
                165                 170                 175

Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Asp Val Val Lys
            180                 185                 190

Arg Cys Pro Asn His Glu Leu Gly Arg Asp Phe Asn Glu Gly Gln Ser
        195                 200                 205

Ala Pro Ala Ser His Leu Ile Arg Val Glu Gly Asn Asn Leu Ser Gln
    210                 215                 220

Tyr Val Asp Asp Pro Val Thr Gly Arg Gln Ser Val Val Val Pro Tyr
225                 230                 235                 240

Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Ile Leu Tyr Asn Phe
                245                 250                 255

Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu
            260                 265                 270

Ile Ile Ile Thr Leu Glu Met Arg Asp Gly Gln Val Leu Gly Arg Arg
        275                 280                 285

Ser Phe Glu Gly Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala
    290                 295                 300

Asp Glu Asp His Tyr Arg Glu Gln Gln Ala Leu Asn Glu Ser Ser Ala
305                 310                 315                 320
```

```
Lys Asn Gly Ala Ala Ser Lys Arg Ala Phe Lys Gln Ser Pro Pro Ala
                325                 330                 335

Val Pro Ala Leu Gly Ala Gly Val Lys Lys Arg Arg His Gly Asp Glu
            340                 345                 350

Asp Thr Tyr Tyr Leu Gln Val Arg Gly Arg Glu Asn Phe Glu Ile Leu
        355                 360                 365

Met Lys Leu Lys Glu Ser Leu Glu Leu Met Glu Leu Val Pro Gln Pro
    370                 375                 380

Leu Val Asp Ser Tyr Arg Gln Gln Gln Gln Leu Leu Gln Arg Pro Ser
385                 390                 395                 400

His Leu Gln Pro Pro Ser Tyr Gly Pro Val Leu Ser Pro Met Asn Lys
                405                 410                 415

Val His Gly Gly Met Asn Lys Leu Pro Ser Val Asn Gln Leu Val Gly
            420                 425                 430

Gln Pro Pro Pro His Ser Ser Ala Ala Thr Pro Asn Leu Gly Pro Val
        435                 440                 445

Gly Pro Gly Met Leu Asn Asn His Gly His Ala Val Pro Ala Asn Gly
    450                 455                 460

Glu Met Ser Ser Ser His Ser Ala Gln Ser Met Val Ser Gly Ser His
465                 470                 475                 480

Cys Thr Pro Pro Pro Pro Tyr His Ala Asp Pro Ser Leu Val Arg Thr
                485                 490                 495

Trp Gly Pro
```

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

GCGAGCTGCC CTCGGAG 17

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

GGTTCTGCAG GTGACTCAG 19

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

GCCATGCCTG TCTACAAG 18

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

ACCAGCTGGT TGACGGAG 18

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

GTCAACCAGC TGGTGGGCCA G 21

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

GTGGATCTCG GCCTCC 16

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

AGGCCGGCGT GGGGAAG 17

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

CTTGGCGATC TGGCAGTAG 19

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

GCGGCCACGA CCGTGAC 17

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

GGCAGCTTGG GTCTCTGG 18

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

CTGTACGTCG GTGACCCC 18

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

TCAGTGGATC TCGGCCTC 18

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

AGGGGACGCA GCGAAACC 18

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

CCATCAGCTC CAGGCTCTC 19

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

CCAGGACAGG CGCAGATG 18

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

GATGAGGTGG CTGGCTGGA 19

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

TGGTCAGGTT CTGCAGGTG 19

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

CACCTACTCC AGGGATGC 18

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

AGGAAAATAG AAGCGTCAGT C 21

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

CAGGCCCACT TGCCTGCC 18

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

CTGTCCCCAA GCTGATGAG 19

CLAIMS

1. Purified polypeptide, comprising an amino acid sequence selected from the group consisting of:

a) the sequence SEQ ID No. 2;
b) the sequence SEQ ID No. 4;
c) the sequence SEQ ID No. 6;
d) the sequence SEQ ID No. 8;
e) the sequence SEQ ID No. 10;
f) the sequence SEQ ID No. 13;
g) the sequence SEQ ID No. 15;
h) the sequence SEQ ID No. 17;
i) the sequence SEQ ID No. 19;

and j) any biologically active sequence derived from SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19.

2. Polypeptide according to Claim 1, characterized in that it comprises the amino acid sequence selected from the group consisting of SEQ ID No. 6, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and SEQ ID No. 19.

3. Polypeptide according to Claim 1, characterized in that it comprises the sequence lying between:
- residue 110 and residue 310 of SEQ ID No. 2 or 6;
- residue 60 and residue 260 of SEQ ID No. 8.

4. Polypeptide according to Claim 1, characterized in that it results from an alternative splicing of the messenger RNA of the corresponding gene.

5. Polypeptide according to any one of the preceding claims, characterized in that it is a recombinant polypeptide produced in the form of a fusion protein.

6. Isolated nucleic acid sequence coding for a polypeptide according to any one of the preceding claims.

7. Isolated nucleic acid sequence according to Claim 6, characterized in that it is selected from the group consisting of :

a) the sequence SEQ ID No. 1;
b) the sequence SEQ ID No. 3;
c) the sequence SEQ ID No. 5;

d) the sequence SEQ ID No. 7;

e) the sequence SEQ ID No. 9;

f) the sequence SEQ ID No. 11;

g) the sequence SEQ ID No. 12;

h) the sequence SEQ ID No. 14;

i) the sequence SEQ ID No. 16;

j) the sequence SEQ ID No. 18;

k) the nucleic acid sequences capable of hybridizing specifically with the sequence SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5, SEQ ID No. 7, SEQ ID No. 9, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 14, SEQ ID No. 16 or SEQ ID No. 18 or with the sequences complementary to them, or of hybridizing specifically with their proximal sequences;

and l) the sequences derived from the sequences a), b), c), d), e), f), g), h), i), j) or k) as a result of the degeneracy of the genetic code, mutation, deletion, insertion, and alternative splicing or an allelic variability.

8. Nucleotide sequence according to Claim 6, characterized in that it is a sequence selected from SEQ ID No. 5, SEQ ID No. 12, SEQ ID No. 14, SEQ ID No. 16 and SEQ ID No. 18 coding, respectively, for the polypeptide of sequences SEQ ID No. 6, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and SEQ ID No. 19.

9. Cloning and/or expression vector containing a nucleic acid sequence according to any one of Claims 6 to 8.

10. Vector according to Claim 9, characterized in that it is the plasmid pSE1.

11. Host cell transfected by a vector according to Claim 9 or 10.

12. Transfected host cell according to Claim 11, characterized in that it is *E. coli* MC 1061.

13. Nucleotide probe or nucleotide primer, characterized in that it hybridizes specifically with any one of the sequences according to Claims 6 to 8 or the sequences complementary to them or the corresponding messenger RNAs or the corresponding genes.

14. Probe or primer according to Claim 13, characterized in that it contains at least 16 nucleotides.

15. Probe or primer according to Claim 13, characterized in that it comprises the whole of the sequence of the gene coding for one of the polypeptides of Claim 1.

16. Nucleotide probe or primer selected from the group consisting of the following oligonucleotides or sequences complementary to them:

SEQ ID No. 20: GCG AGC TGC CCT CGG AG
SEQ ID No. 21: GGT TCT GCA GGT GAC TCA G
SEQ ID No. 22: GCC ATG CCT GTC TAC AAG
SEQ ID No. 23: ACC AGC TGG TTG ACG GAG
SEQ ID No. 24: GTC AAC CAG CTG GTG GGC CAG
SEQ ID No. 25: GTG GAT CTC GGC CTC C
SEQ ID No. 26: AGG CCG GCG TGG GGA AG
SEQ ID No. 27: CTT GGC GAT CTG GCA GTA G
SEQ ID No. 28: GCG GCC ACG ACC GTG AC
SEQ ID No. 29: GGC AGC TTG GGT CTC TGG
SEQ ID No. 30: CTG TAC GTC GGT GAC CCC
SEQ ID No. 31: TCA GTG GAT CTC GGC CTC
SEQ ID No. 32: AGG GGA CGC AGC GAA ACC
SEQ ID No. 33: CCA TCA GCT CCA GGC TCT C
SEQ ID No. 34: CCA GGA CAG GCG CAG ATG
SEQ ID No. 35: GAT GAG GTG GCT GGC TGG A
SEQ ID No. 36: TGG TCA GGT TCT GCA GGT G
SEQ ID No. 37: CAC CTA CTC CAG GGA TGC
SEQ ID No. 38: AGG AAA ATA GAA GCG TCA GTC
SEQ ID No. 39: CAG GCC CAC TTG CCT GCC
and SEQ ID No. 40: CTG TCC CCA AGC TGA TGA G

17. Use of a sequence according to any one of Claims 6 to 8, for the manufacture of oligonucleotide primers for sequencing reactions or specific amplification reactions according to the PCR technique or any variant of the latter.

18. Nucleotide primer pair, characterized in that it comprises the primers selected from the group consisting of the following sequences:

a) sense primer: GCG AGC TGC CCT CGG AG (SEQ ID No. 20)
antisense primer: GGT TCT GCA GGT GAC TCA G (SEQ ID No. 21)

b) sense primer: GCC ATG CCT GTC TAC AAG (SEQ ID No. 22)
antisense primer: ACC AGC TGG TTG ACG GAG (SEQ ID No. 23)

c) sense primer: GTC AAC CAG CTG GTG GGC CAG (SEQ ID No. 24)
antisense primer: GTG GAT CTC GGC CTC C (SEQ ID No. 25)

d) sense primer: AGG CCG GCG TGG GGA AG (SEQ ID No. 26)
antisense primer: CTT GGC GAT CTG GCA GTA G (SEQ ID No. 27)

e) sense primer: GCG GCC ACG ACC GTG A (SEQ ID No. 28)
antisense primer: GGC AGC TTG GGT CTC TGG (SEQ ID No. 29)

f) sense primer: CTG TAC GTC GGT GAC CCC (SEQ ID No. 30)
antisense primer: TCA GTG GAT CTC GGC CTC (SEQ ID No. 31)

g) sense primer: AGG GGA CGC AGC GAA ACC (SEQ ID No. 32)
antisense primer: GGC AGC TTG GGT CTC TGG (SEQ ID No. 29)

h) sense primer: CCCCCCCCCCCCCCN (where N equals G, A or T)
antisense primer: CCA TCA GCT CCA GGC TCT C (SEQ ID No. 33)

i) sense primer: CCCCCCCCCCCCCCN (where N equals G, A or T)
antisense primer: CCA GGA CAG GCG CAG ATG (SEQ ID No. 34)

j) sense primer: CCCCCCCCCCCCCCCN (where N equals G, A or T)
antisense primer: CTT GGC GAT CTG GCA GTA G (SEQ ID No. 27)

k) sense primer: CAC CTA CTC CAG GGA TGC (SEQ ID No. 37)
antisense primer: AGG AAA ATA GAA GCG TCA GTC (SEQ ID No. 38)

and l) sense primer: CAG GCC CAC TTG CCT GCC (SEQ ID No. 39)
antisense primer: CTG TCC CCA AGC TGA TGA G (SEQ ID No. 40)

19. Use of a sequence according to any one of Claims 6 to 8, which is usable in gene therapy.

20. Use of a sequence according to any one of Claims 6 to 8, for the production of diagnostic

nucleotide probes or primers, or of antisense sequences which are usable in gene therapy.

21. Use of nucleotide primers according to any one of Claims 6 to 8, for sequencing.

22. Use of a probe or primer according to any one of Claims 13 to 16, as an *in vitro* diagnostic tool for the detection, by hybridization experiments, of nucleic acid sequences coding for a polypeptide according to any one of Claims 1 to 4, in biological samples, or for the demonstration of aberrant syntheses or of genetic abnormalities.

23. Method of *in vitro* diagnosis for the detection of aberrant syntheses or of genetic abnormalities in the nucleic acid sequences coding for a polypeptide according to any one of Claims 1 to 4, characterized in that it comprises:

- the bringing of a nucleotide probe according to any one of Claims 13 to 16 into contact with a biological sample under conditions permitting the formation of a hybridization complex between the said probe and the abovementioned nucleotide sequence, where appropriate after a prior step of amplification of the abovementioned nucleotide sequence;
- the detection of the hybridization complex possibly formed;
- where appropriate, the sequencing of the nucleotide sequence forming the hybridization complex with the probe of the invention.

24. Use of a nucleic acid sequence according to any one of Claims 6 to 8, for the production of a recombinant polypeptide according to any one of Claims 1 to 5.

25. Method of production of a recombinant SR-p70 protein, characterized in that transfected cells according to Claim 10 or 11 are cultured under conditions permitting the expression of a recombinant polypeptide of sequence SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 or SEQ ID No. 19 or any

biologically active fragment or derivative, and in that the said recombinant polypeptide is recovered.

26. Mono- or polyclonal antibodies or their fragments, chimeric antibodies or immunoconjugates, characterized in that they are capable of specifically recognizing a polypeptide according to any one of Claims 1 to 4.

27. Use of the antibodies according to the preceding claim, for the purification or detection of a polypeptide according to any one of Claims 1 to 4 in a biological sample.

28. Method of *in vitro* diagnosis of pathologies correlated with an expression or an abnormal accumulation of SR-p70 proteins, in particular the phenomena of carcinogenesis, from a biological sample, characterized in that at least one antibody according to Claim 25 is brought into contact with the said biological sample under conditions permitting the possible formation of specific immunological complexes between an SR-p70 protein and the said antibody or antibodies, and in that the specific immunological complexes possibly formed are detected.

29. Kit for the *in vitro* diagnosis of an expression or an abnormal accumulation of SR-p70 proteins in a biological sample and/or for measuring the level of expression of these proteins in the said sample, comprising:

- at least one antibody according to Claim 25, optionally bound to a support,
- means of visualization of the formation of specific antigen-antibody complexes between an SR-p70 protein and the said antibody, and/or means of quantification of these complexes.

30. Method for the early diagnosis of tumour formation, characterized in that autoantibodies directed against an SR-p70 protein are demonstrated in a serum sample drawn from an individual, according to the steps that consist in bringing a serum sample drawn from an individual into contact with a polypeptide of the invention, optionally bound to a support, under

conditions permitting the formation of specific immunological complexes between the said polypeptide and the autoantibodies possibly present in the serum sample, and in that the specific immunological complexes possibly formed are detected.

31. Method of determination of an allelic variability, a mutation, a deletion, an insertion, a loss of heterozygosity or a genetic abnormality of the SR-p70 gene, characterized in that it utilizes at least one nucleotide sequence according to any one of Claims 6 to 8.

32. Method of determination of an allelic variability of the SR-p70 gene at position -30 and -20 relative to the initiation ATG of exon 2 which may be involved in pathologies, and characterized in that it comprises at least:

- a step during which exon 2 of the SR-p70 gene carrying the target sequence is amplified by PCR using a pair of oligonuclotide primers according to any one of Claims 6 to 8;
- a step during which the amplified products are treated with a restriction enzyme whose cleavage site corresponds to the allele sought;
- a step during which at least one of the products of the enzyme reaction is detected or assayed.

33. Pharmaceutical composition comprising as active principle a polypeptide according to any one of Claims 1 to 4.

34. Pharmaceutical composition according to the preceding claim, characterized in that it comprises a polypeptide according to Claim 2.

35. Pharmaceutical composition containing an inhibitor or an activator of SR-p70 activity.

36. Pharmaceutical composition containing a polypeptide derived from a polypeptide according to any one of Claims 1 to 5, characterized in that it is an inhibitor or an activator of SR-p70.

```
  1 TGCCTCCCCGCCCGCGCACCCGCCCCGAGGCCTGTGCTCCTGCGAAGGGG  50
  1 ......................................GGGGCTCCGGGG  12

 51 ACGCAGCGAAGCCGGGGCCCGCGCCAGGCCGGCCGGGACGGACGCCGATG 100
 13 ACACTTGGCGTCCGGGCTGGAAGCGTGCTTTCCAAGACGGTGACACGCTT  62

101 CCCGGAGCTGCGACGGCTGCAGAGCGAGCTGCCCTCGGAGGCCGGTGTGA 150
 63 CCCTGAGGATTGGCAGCCAGACTGCTTACGGTCAC...TGCCATGGAGG 109

151 GGAAGATGGCCCAGTCCACCACCACCTCCCCCGATGGGGCACCACGTTT 200
110 AGCCGCAGTCAGATCCCAGCATCGAGCCCCCTCTGAGTCAGGAAACATTT 159

201 GAGCACCTCTGGAGCTCTCTGGAACCAGACAGCACCTACTTCGACCTTCC 250
160 TCAGACCTATGGAAACTACTTCCTGAAAACAAC.GTTCTGTCCCCCTTGC 208

251 CCAGTCAAGCCGGGGGAATAATGAGGTGGTGGGTGGCACGGATTCCAGCA 300
209 CGTCCCAAGCGGTGGATGATTTGATGCTCTCTCCGGATGATCTTGCACAA 258

301 TGGACGTCTTCCACCTAGAGGGCATGACCACATCTGTCATGGCCCAGTTC 350
259 TGG............................TTAACTGAAGACCCAGGTC 280

351 AATTTGCTGAGCAGCACCATGGACCAGATGAGCAGCCGCGCTGCCTCGGC 400
281 CAGATGAAGCTC...........CCAGAATGTCAGAGGCTGCTCCCCACA 319

401 CAGCCCGTACACCCCGGAGCACGCCGCCAGCGTGCCCACCCATTCACCCT 450
320 TGGCCCCCACACCAGCAGCTCCTACACCGGCGGCCCCTGCACCAGCCCC. 368

451 ACGCACAGCCCAGCTCCACCTTCGACACCATGTCGCCCGCGCCTGTCATC 500
369 .........................CTCCTGGCCCCTGTCATCCTCTGTC 393

501 CCCTCCAACACCGACTATCCCGGACCCCACCACTTCGAGGTCACTTTCCA 550
394 CCTTCCCAGAAAACCTACCACGGCAGCTACGGTTTCCGTCTGGGCTTCCT 443

551 GCAGTCCAGCACGGCCAAGTCAGCCACCTGGACGTACTCCCCACTCTTGA 600
444 GCATTCTGGAACAGCCAAGTCTGTGACTTGCACGTACTCCCCTGACCTCA 493

601 AGAAACTCTACTGCCAGATCGCCAAGACATGCCCCATCCAGATCAAGGTG 650
494 ACAAGATGTTTTGCCAGCTGGCCAAGACCTGCCCCGTGCAGCTGTGGGTT 543

651 TCCGCCCCACCGCCCCCGGGCACCGCCATCCGGGCCATGCCTGTCTACAA 700
544 GATTCCACACCCCCGCCCGGCAGCCGCGTCCGCGCCATGGCCATCTACAA 593

701 GAAGGCGGAGCACGTGACCGACATCGTGAAGCGCTGCCCCAACCACGAGC 750
594 GCAGTCACAGCACATGACTGAGGTCGTGAGGCGCTGCCCCCACCATGAGC 643

751 TCGGGAGGGACTTCAACGAAGGACAGTCTGCCCCAGCCAGCCACCTCATC 800
644 GCTGCTCAGACAGCGATGGA......CTGGCCCCTCCTCAACATCTTATC 687

801 CGTGTGGAAGGCAATAATCTCTCGCAGTATGTGGACGACCCTGTCACCGG 850
688 CGAGTGGAAGGAAATTTGCGTGTGGAGTATTCGGATGACAGAAACACTTT 737

851 CAGGCAGAGCGTCGTGGTGCCCTATGAGCCACCACAGGTGGGGACAGAAT 900
738 TCGACATAGTGTGGTGGTGCCCTATGAGCCGCCTGAGGTTGGCTCTGACT 787
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FIG.1

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 901 TCACCACCATCCTGTACAACTTCATGTGTAACAGCAGCTGTGTGGGGGGC  950
 788 GTACCACCATCCACTACAACTACATGTGTAACAGTTCCTGCATGGGCGGC  837

 951 ATGAACCGACGGCCCATCCTCATCATCATCACCCTGGAGACGCGGGATGG 1000
 838 ATGAACCGGAGGCCCATCCTCACAATTATCACACTGGAAGACTCCAGTGG  887

1001 GCAGGTGCTGGGCCGCCGGTCCTTCGAGGGCCGCATCTGCGCCTGTCCTG 1050
 888 TAATCTACTGGGACGGAACAGCTTTGAGGTGCGAGTTTGTGCCTGTCCTG  937

1051 GCCGCGACCGAAAAGCCGATGAGGACCACTACCGGGAGCAGCAGGCCTTG 1100
 938 GGAGAGACCGGCGCACAGAGGAAGAGAATTTCC.................G  971

1101 AATGAGAGCTCCGCCAAGAACGGGGCTGCCAGCAAGCGCGCCTTCAAGCA 1150
 972 CAAGAAAGGGGAGCCTTGCCACGAGCTGCCCCCTGGGAGCACTAAGCGAG 1021

1151 GAGTCCCCCTGCCGTCCCCGCCCTGGGCCC.GGGTGTGAAGAAGCGGCGG 1199
1022 CACTGCCCAACAACACCAGCTCCTCTCCCCAGCCAAAGAAGAAACCACTG 1071

1200 CACGGAGACGAGGACACGTACTACCTGCAGGTGCGAGGCCGCGAGAACTT 1249
1072 GATGGAGAATATTTCAC......CCTTCAGATCCGCGGGCGTGAGCGCTT 1115

1250 CGAGATCCTGATGAAGCTGAAGGAGAGCCTGGAGCTGATGGAGTTGGTGC 1299
1116 CGAGATGTTCCGAGAGCTGAATGAGGCCTTGGAACTCAAGGA........ 1157

1300 CGCAGCCGCTGGTAGACTCCTATCGGCAGCAGCAGCAGCTCCTACAGAGG 1349
1158 TGCCCAGGCTGGGAAAGAGCCAGCGG..GGAGCAGGGCTCACTCCAGCCA 1205

1350 CCGAGTCACCTACAGCCCCCATCCTACGGGCCGGTCCTCTCGCCCATGAA 1399
1206 CCTGAAGTCCAAGAAGGGGCAATCTACCTCCCGCCATAAAAAATTCATGT 1255

1400 CAAGGTGCACGGGGGCGTGAACAAGCTGCCCTCCGTCAACCAGCTGGTGG 1449
1256 TCAAGACAGAGGGGCCTGACTCAGACTGACATTC.....TCAGCTTCTTG 1300

1450 GCCAGCCTCCCCCGCACAGCTCGGCAGCTACACCCAACCTGGGACCTGTG 1499
1301 TTCCCCCACTGAGCCTCCCACCCCCATCT.CTCCCTCCCCTGCCATTTTG 1349

1500 GGCTCTGGGATGCTCAACAACCACGGCCACGCAGTGCCAGCCAACAGCGA 1549
1350 AGTTCTGGGTCTTTAAACCCTTGCTTGCAATAGGTGTGTGTCAGAAGCAA 1399

1550 GATGACCAGCAGCCACGGCACCCAGTCCATGGTCTCGGGGTCCCACTGCA 1599
1400 A................................................. 1400
```

FIG.1 cont.

```
  1 MAQSTTTSPDGGTTFEHLWSSLEPDSTYFDLPQSSRGNNEVVGGTDSSMD  50
  1 .....MEEPQSDPSIEPPLS....QETFSDLWKLLPENNVLSPLPSQAVD  41

 51 VFHLEGMTTSVMAQFNLLSSTMDQMSSRAASASPYTPEHAASVPTHSPYA 100
 42 DLML...SPDDLAQWLTEDPGPDEAPRMSEAAPHMAPTPAAPTPA.APAP  87

101 QPSSTFDTMSPAPVIPSNTDYPGPHHFEVTFQQSSTAKSATWTYSPLLKK 150
 88 APSWPL.....SSSVPSQKTYHGSYGFRLGFLHSGTAKSVTCTYSPDLNK 132

151 LYCQIAKTCPIQIKVSAPPPPGTAIRAMPVYKKAEHVTDIVKRCPNHELG 200
133 MFCQLAKTCPVQLWVDSTPPPGSRVRAMAIYKQSQHMTEVVRRCPHHE.. 180

201 RDFNEGQSAPASHLIRVEGNNLSQYVDDPVTGRQSVVVPYEPPQVGTEFT 250
181 RCSDSDGLAPPQHLIRVEGNLRVEYSDDRNTFRHSVVVPYEPPEVGSDCT 230

251 TILYNFMCNSSCVGGMNRRPILIIITLETRDGQVLGRRSFEGRICACPGR 300
231 TIHYNYMCNSSCMGGMNRRPILTIITLEDSSGNLLGRNSFEVRVCACPGR 280

301 DRKADEDHYREQQALNESSAKNGAASKRAFKQSPPAVPALGPGVKKRRHG 350
281 DRRTEEENFRKKG..EPCHELPPGSTKRALPNNTSSSPQ.....PKKKPL 323

351 DEDTYYLQVRGRENFEILMKLKESLELMELVPQPLVDSYRQQQQLLQRPS 400
324 DGEYFTLQIRGRERFEMFRELNEALELKDAQAGKEPAGSRAHSSHLKSKK 373

401 HLQPPSYGPVLSPMNKVHGGVNKLPSVNQLVGQPPPHSSAATPNLGPVGS 450
374 GQSTSRHKKFMFKTEGPDSD..............................  393
```

FIG. 2

```
  1 TGCCTCCCCGCCCGCGCACCCGCCCCGAGGCCTGTGCTCCTGCGAAGGGG 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 TGCCTCCCCGCCCGCGCACCCGCCCCGAGGCCTGTGCTCCTGCGAAGGGG 50

 51 ACGCAGCGAAGCCGGGGCCCGCGCCAGGCCGGCCGGGACGGACGCCGATG 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 ACGCAGCGAAGCCGGGGCCCGCGCCAGGCCGGCCGGGACGGACGCCGATG 100

101 CCCGGAGCTGCGACGGCTGCAGAGCGAGCTGCCCTCGGAGGCCGGTGTGA 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 CCCGGAGCTGCGACGGCTGCAGAGCGAGCTGCCCTCGGAGGCCGGTGTGA 150

151 GGAAGATGGCCCAGTCCACCACCACCTCCCCCGATGGGGGCACCACGTTT 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 GGAAGATGGCCCAGTCCACCACCACCTCCCCCGATGGGGGCACCACGTTT 200

201 GAGCACCTCTGGAGCTCTCTGGAACCAGACAGCACCTACTTCGACCTTCC 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 GAGCACCTCTGGAGCTCTCTGGAACCAGACAGCACCTACTTCGACCTTCC 250

251 CCAGTCAAGCCGGGGGAATAATGAGGTGGTGGGTGGCACGGATTCCAGCA 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 CCAGTCAAGCCGGGGGAATAATGAGGTGGTGGGTGGCACGGATTCCAGCA 300

301 TGGACGTCTTCCACCTAGAGGGCATGACCACATCTGTCATGGCCCAGTTC 350
    ||||||||||||||||||||||||||||||||||||||||||||||||||
301 TGGACGTCTTCCACCTAGAGGGCATGACCACATCTGTCATGGCCCAGTTC 350

351 AATTTGCTGAGCAGCACCATGGACCAGATGAGCAGCCGCGCTGCCTCGGC 400
    ||||||||||||||||||||||||||||||||||||||||||||||||||
351 AATTTGCTGAGCAGCACCATGGACCAGATGAGCAGCCGCGCTGCCTCGGC 400

401 CAGCCCGTACACCCCGGAGCACGCCGCCAGCGTGCCCACCCATTCACCCT 450
    ||||||||||||||||||||||||||||||||||||||||||||||||||
401 CAGCCCGTACACCCCGGAGCACGCCGCCAGCGTGCCCACCCATTCACCCT 450

451 ACGCACAGCCCAGCTCCACCTTCGACACCATGTCGCCCGCGCCTGTCATC 500
    ||||||||||||||||||||||||||||||||||||||||||||||||||
451 ACGCACAGCCCAGCTCCACCTTCGACACCATGTCGCCCGCGCCTGTCATC 500

501 CCCTCCAACACCGACTATCCCGGACCCCACCACTTCGAGGTCACTTTCCA 550
    ||||||||||||||||||||||||||||||||||||||||||||||||||
501 CCCTCCAACACCGACTATCCCGGACCCCACCACTTCGAGGTCACTTTCCA 550

551 GCAGTCCAGCACGGCCAAGTCAGCCACCTGGACGTACTCCCCACTCTTGA 600
    ||||||||||||||||||||||||||||||||||||||||||||||||||
551 GCAGTCCAGCACGGCCAAGTCAGCCACCTGGACGTACTCCCCACTCTTGA 600

601 AGAAACTCTACTGCCAGATCGCCAAGACATGCCCCATCCAGATCAAGGTG 650
    ||||||||||||||||||||||||||||||||||||||||||||||||||
601 AGAAACTCTACTGCCAGATCGCCAAGACATGCCCCATCCAGATCAAGGTG 650

651 TCCGCCCCACCGCCCCCGGGCACCGCCATCCGGGCCATGCCTGTCTACAA 700
    ||||||||||||||||||||||||||||||||||||||||||||||||||
651 TCCGCCCCACCGCCCCCGGGCACCGCCATCCGGGCCATGCCTGTCTACAA 700

701 GAAGGCGGAGCACGTGACCGACATCGTGAAGCGCTGCCCCAACCACGAGC 750
    ||||||||||||||||||||||||||||||||||||||||||||||||||
701 GAAGGCGGAGCACGTGACCGACATCGTGAAGCGCTGCCCCAACCACGAGC 750

751 TCGGGAGGGACTTCAACGAAGGACAGTCTGCCCCAGCCAGCCACCTCATC 800
    ||||||||||||||||||||||||||||||||||||||||||||||||||
751 TCGGGAGGGACTTCAACGAAGGACAGTCTGCCCCAGCCAGCCACCTCATC 800

801 CGTGTGGAAGGCAATAATCTCTCGCAGTATGTGGACGACCCTGTCACCGG 850
    ||||||||||||||||||||||||||||||||||||||||||||||||||
801 CGTGTGGAAGGCAATAATCTCTCGCAGTATGTGGACGACCCTGTCACCGG 850

851 CAGGCAGAGCGTCGTGGTGCCCTATGAGCCACCACAGGTGGGGACAGAAT 900
    ||||||||||||||||||||||||||||||||||||||||||||||||||
851 CAGGCAGAGCGTCGTGGTGCCCTATGAGCCACCACAGGTGGGGACAGAAT 900
```

FIG.3 cont.

```
 901 TCACCACCATCCTGTACAACTTCATGTGTAACAGCAGCTGTGTGGGGGGC  950
     ||||||||||||||||||||||||||||||||||||||||||||||||||
 901 TCACCACCATCCTGTACAACTTCATGTGTAACAGCAGCTGTGTGGGGGGC  950

 951 ATGAACCGACGGCCCATCCTCATCATCATCACCCTGGAGACGCGGGATGG 1000
     ||||||||||||||||||||||||||||||||||||||||||||||||||
 951 ATGAACCGACGGCCCATCCTCATCATCATCACCCTGGAGACGCGGGATGG 1000

1001 GCAGGTGCTGGGCCGCCGGTCCTTCGAGGGCCGCATCTGCGCCTGTCCTG 1050
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1001 GCAGGTGCTGGGCCGCCGGTCCTTCGAGGGCCGCATCTGCGCCTGTCCTG 1050

1051 GCCGCGACCGAAAAGCCGATGAGGACCACTACCGGGAGCAGCAGGCCTTG 1100
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1051 GCCGCGACCGAAAAGCCGATGAGGACCACTACCGGGAGCAGCAGGCCTTG 1100

1101 AATGAGAGCTCCGCCAAGAACGGGGCTGCCAGCAAGCGCGCCTTCAAGCA 1150
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1101 AATGAGAGCTCCGCCAAGAACGGGGCTGCCAGCAAGCGCGCCTTCAAGCA 1150

1151 GAGTCCCCCTGCCGTCCCCGCCCTGGGCCCGGGTGTGAAGAAGCGGCGGC 1200
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1151 GAGTCCCCCTGCCGTCCCCGCCCTGGGCCCGGGTGTGAAGAAGCGGCGGC 1200

1201 ACGGAGACGAGGACACGTACTACCTGCAGGTGCGAGGCCGCGAGAACTTC 1250
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1201 ACGGAGACGAGGACACGTACTACCTGCAGGTGCGAGGCCGCGAGAACTTC 1250

1251 GAGATCCTGATGAAGCTGAAGGAGAGCCTGGAGCTGATGGAGTTGGTGCC 1300
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1251 GAGATCCTGATGAAGCTGAAGGAGAGCCTGGAGCTGATGGAGTTGGTGCC 1300

1301 GCAGCCGCTGGTAGACTCCTATCGGCAGCAGCAGCAGCTCCTACAGAGGC 1350
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1301 GCAGCCGCTGGTAGACTCCTATCGGCAGCAGCAGCAGCTCCTACAGAGGC 1350

1351 CGAGTCACCTACAGCCCCCATCCTACGGGCCGGTCCTCTCGCCCATGAAC 1400
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1351 CGAGTCACCTACAGCCCCCATCCTACGGGCCGGTCCTCTCGCCCATGAAC 1400

1401 AAGGTGCACGGGGGCGTGAACAAGCTGCCCTCCGTCAACCAGCTGGTGGG 1450
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1401 AAGGTGCACGGGGGCGTGAACAAGCTGCCCTCCGTCAACCAGCTGGTGGG 1450

1451 CCAGCCTCCCCCGCACAGCTCGGCAGCTACACCCAACCTGGGACCTGTGG 1500
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1451 CCAGCCTCCCCCGCACAGCTCGGCAGCTACACCCAACCTGGGACCTGTGG 1500

1501 GCTCTGGGATGCTCAACAACCACGGCCACGCAGTGCCAGCCAACAGCGAG 1550
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1501 GCTCTGGGATGCTCAACAACCACGGCCACGCAGTGCCAGCCAACAGCGAG 1550

1551 ATGACCAGCAGCCACGGCACCCAGTCCATGGTCTCGGGGTCCCACTGCAC 1600
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1551 ATGACCAGCAGCCACGGCACCCAGTCCATGGTCTCGGGGTCCCACTGCAC 1600

1601 TCCGCCACCCCCCTACCACGCCGACCCCAGCCTCGTCAGTTTTTTAACAG 1650
     |||||||||||||||||||||||||||||||||||||
1601 TCCGCCACCCCCCTACCACGCCGACCCCAGCCTCGTC............. 1637

                                .
                                .
                                .

1701 AGCATTTACCACCTGCAGAACCTGACCATCGAGGACCTGGGGGCCCTGAA 1750
                                   |||||||||||||||||||
1638 ...............................AGGACCTGGGGGCCCTGAA 1656

1751 GATCCCCGAGCAGTATCGCATGACCATCTGGCGGGGCCTGCAGGACCTGA 1800
     ||||||||||||||||||||||||||||||||||||||||||||||||||
```

FIG.3 cont.

```
1657 GATCCCCGAGCAGTATCGCATGACCATCTGGCGGGGCCTGCAGGACCTGA 1706

1801 AGCAGGGCCACGACTACGGCGCCGCCGCGCAGCAGCTGCTCCGCTCCAGC 1850
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1707 AGCAGGGCCACGACTACGGCGCCGCCGCGCAGCAGCTGCTCCGCTCCAGC 1756

1851 AACGCGGCCGCCATTTCCATCGGCGGCTCCGGGGAGCTGCAGCGCCAGCG 1900
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1757 AACGCGGCCGCCATTTCCATCGGCGGCTCCGGGGAGCTGCAGCGCCAGCG 1806

1901 GGTCATGGAGGCCGTGCACTTCCGCGTGCGCCACACCATCACCATCCCCA 1950
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1807 GGTCATGGAGGCCGTGCACTTCCGCGTGCGCCACACCATCACCATCCCCA 1856

1951 ACCGCGGCGGCCCCGGCGCCGGCCCCGACGAGTGGGCGGACTTCGGCTTC 2000
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1857 ACCGCGGCGGCCCCGGCGCCGGCCCCGACGAGTGGGCGGACTTCGGCTTC 1906

2001 GACCTGCCCGACTGCAAGGCCCGCAAGCAGCCCATCAAGGAGGAGTTCAC 2050
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1907 GACCTGCCCGACTGCAAGGCCCGCAAGCAGCCCATCAAGGAGGAGTTCAC 1956

2051 GGAGGCCGAGATCCACTGAGGGGCCGGGCCCAGCCAGAGCCTGTGCCACC 2100
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1957 GGAGGCCGAGATCCACTGAGGGGCCGGGCCCAGCCAGAGCCTGTGCCACC 2006

2101 GCCCAGAGACCCAGGCCGCCTCGCTCTC 2128
     ||||||||||||||||||||||||||||
2007 GCCCAGAGACCCAGGCCGCCTCGCTCTC 2034
```

FIG.3cont.

```
   1  TGCCTCCCCGCCCGCGCACCCGCCCCGAGGCCTGTGCTCCTGCGAAGGGGACGCAGCGAA   60
  61  GCCGGGGCCCGCGCCAGGCCGGCCGGGACGGACGCCGATGCCCGGAGCTGCGACGGCTGC  120
 121  AGAGCGAGCTGCCCTCGGAGGCCGGTGTGAGGAAGATGGCCCAGTCCACCACCACCTCCC  180
 -10                                       M  A  Q  S  T  T  T  S  P    9
 181  CCGATGGGGGCACCACGTTTGAGCACCTCTGGAGCTCTCTGGAACCAGACAGCACCTACT  240
  10    D  G  G  T  T  F  E  H  L  W  S  S  L  E  P  D  S  T  Y  F   29
 241  TCGACCTTCCCCAGTCAAGCCGGGGGAATAATGAGGTGGTGGGTGGCACGGATTCCAGCA  300
  30    D  L  P  Q  S  S  R  G  N  N  E  V  V  G  G  T  D  S  S  M   49
 301  TGGACGTCTTCCACCTAGAGGGCATGACCACATCTGTCATGGCCCAGTTCAATTTGCTGA  360
  50    D  V  F  H  L  E  G  M  T  T  S  V  M  A  Q  F  N  L  L  S   69
 361  GCAGCACCATGGACCAGATGAGCAGCCGCGCTGCCTCGGCCAGCCCGTACACCCCGGAGC  420
  70    S  T  M  D  Q  M  S  S  R  A  A  S  A  S  P  Y  T  P  E  H   89
 421  ACGCCGCCAGCGTGCCCACCCATTCACCCTACGCACAGCCCAGCTCCACCTTCGACACCA  480
  90    A  A  S  V  P  T  H  S  P  Y  A  Q  P  S  S  T  F  D  T  M  109
 481  TGTCGCCCGCGCCTGTCATCCCCTCCAACACCGACTATCCCGGACCCCACCACTTCGAGG  540
 110    S  P  A  P  V  I  P  S  N  T  D  Y  P  G  P  H  H  F  E  V  129
 541  TCACTTTCCAGCAGTCCAGCACGGCCAAGTCAGCCACCTGGACGTACTCCCCACTCTTGA  600
 130    T  F  Q  Q  S  S  T  A  K  S  A  T  W  T  Y  S  P  L  L  K  149
 601  AGAAACTCTACTGCCAGATCGCCAAGACATGCCCCATCCAGATCAAGGTGTCCGCCCCAC  660
 150    K  L  Y  C  Q  I  A  K  T  C  P  I  Q  I  K  V  S  A  P  P  169
 661  CGCCCCCGGGCACCGCCATCCGGGCCATGCCTGTCTACAAGAAGGCGGAGCACGTGACCG  720
 170    P  P  G  T  A  I  R  A  M  P  V  Y  K  K  A  E  H  V  T  D  189
 721  ACATCGTGAAGCGCTGCCCCAACCACGAGCTCGGGAGGGACTTCAACGAAGGACAGTCTG  780
 190    I  V  K  R  C  P  N  H  E  L  G  R  D  F  N  E  G  Q  S  A  209
 781  CCCCAGCCAGCCACCTCATCCGTGTGGAAGGCAATAATCTCTCGCAGTATGTGGACGACC  840
 210    P  A  S  H  L  I  R  V  E  G  N  N  L  S  Q  Y  V  D  D  P  229
 841  CTGTCACCGGCAGGCAGAGCGTCGTGGTGCCCTATGAGCCACCACAGGTGGGGACAGAAT  900
 230    V  T  G  R  Q  S  V  V  V  P  Y  E  P  P  Q  V  G  T  E  F  249
 901  TCACCACCATCCTGTACAACTTCATGTGTAACAGCAGCTGTGTGGGGGGCATGAACCGAC  960
 250    T  T  I  L  Y  N  F  M  C  N  S  S  C  V  G  G  M  N  R  R  269
 961  GGCCCATCCTCATCATCATCACCCTGGAGACGCGGGATGGGCAGGTGCTGGGCCGCCGGT 1020
 270    P  I  L  I  I  I  T  L  E  T  R  D  G  Q  V  L  G  R  R  S  289
1021  CCTTCGAGGGCCGCATCTGCGCCTGTCCTGGCCGCGACCGAAAAGCCGATGAGGACCACT 1080
 290    F  E  G  R  I  C  A  C  P  G  R  D  R  K  A  D  E  D  H  Y  309
1081  ACCGGGAGCAGCAGGCCTTGAATGAGAGCTCCGCCAAGAACGGGGCTGCCAGCAAGCGCG 1140
 310    R  E  Q  Q  A  L  N  E  S  S  A  K  N  G  A  A  S  K  R  A  329
1141  CCTTCAAGCAGAGTCCCCCTGCCGTCCCCGCCCTGGGCCCGGGTGTGAAGAAGCGGCGGC 1200
 330    F  K  Q  S  P  P  A  V  P  A  L  G  P  G  V  K  K  R  R  H  349
1201  ACGGAGACGAGGACACGTACTACCTGCAGGTGCGAGGCCGCGAGAACTTCGAGATCCTGA 1260
 350    G  D  E  D  T  Y  Y  L  Q  V  R  G  R  E  N  F  E  I  L  M  369
1261  TGAAGCTGAAGGAGAGCCTGGAGCTGATGGAGTTGGTGCCGCAGCCGCTGGTAGACTCCT 1320
 370    K  L  K  E  S  L  E  L  M  E  L  V  P  Q  P  L  V  D  S  Y  389
1321  ATCGGCAGCAGCAGCAGCTCCTACAGAGGCCGAGTCACCTACAGCCCCCATCCTACGGGC 1380
 390    R  Q  Q  Q  Q  L  L  Q  R  P  S  H  L  Q  P  P  S  Y  G  P  409
1381  CGGTCCTCTCGCCCATGAACAAGGTGCACGGGGGCGTGAACAAGCTGCCCTCCGTCAACC 1440
 410    V  L  S  P  M  N  K  V  H  G  G  V  N  K  L  P  S  V  N  Q  429
1441  AGCTGGTGGGCCAGCCTCCCCCGCACAGCTCGGCAGCTACACCCAACCTGGGACCTGTGG 1500
 430    L  V  G  Q  P  P  P  H  S  S  A  A  T  P  N  L  G  P  V  G  449
1501  GCTCTGGGATGCTCAACAACCACGGCCACGCAGTGCCAGCCAACAGCGAGATGACCAGCA 1560
 450    S  G  M  L  N  N  H  G  H  A  V  P  A  N  S  E  M  T  S  S  469
1561  GCCACGGCACCCAGTCCATGGTCTCGGGGTCCCACTGCACTCCGCCACCCCCCTACCACG 1620
 470    H  G  T  Q  S  M  V  S  G  S  H  C  T  P  P  P  P  Y  H  A  489
1621  CCGACCCCAGCCTCGTCAGTTTTTTAACAGGATTGGGGTGTCCAAACTGCATCGAGTATT 1680
 490    D  P  S  L  V  S  F  L  T  G  L  G  C  P  N  C  I  E  Y  P  509
```

FIG.4

```
1681  TCACGTCCCAGGGGTTACAGAGCATTTACCACCTGCAGAACCTGACCATCGAGGACCTGG  1740
 510   T  S  Q  G  L  Q  S  I  Y  H  L  Q  N  L  T  I  E  D  L  G   529
1741  GGGCCCTGAAGATCCCCGAGCAGTATCGCATGACCATCTGGCGGGGCCTGCAGGACCTGA  1800
 530   A  L  K  I  P  E  Q  Y  R  M  T  I  W  R  G  L  Q  D  L  K   549
1801  AGCAGGGCCACGACTACGGCGCCGCCGCGCAGCAGCTGCTCCGCTCCAGCAACGCGGCCG  1860
 550   Q  G  H  D  Y  G  A  A  A  Q  Q  L  L  R  S  S  N  A  A  A   569
1861  CCATTTCCATCGGCGGCTCCGGGGAGCTGCAGCGCCAGCGGGTCATGGAGGCCGTGCACT  1920
 570   I  S  I  G  G  S  G  E  L  Q  R  Q  R  V  M  E  A  V  H  F   589
1921  TCCGCGTGCGCCACACCATCACCATCCCCAACCGCGGCGGCCCCGGCGCCGGCCCCGACG  1980
 590   R  V  R  H  T  I  T  I  P  N  R  G  G  P  G  A  G  P  D  E   609
1981  AGTGGGCGGACTTCGGCTTCGACCTGCCCGACTGCAAGGCCCGCAAGCAGCCCATCAAGG  2040
 610   W  A  D  F  G  F  D  L  P  D  C  K  A  R  K  Q  P  I  K  E   629
2041  AGGAGTTCACGGAGGCCGAGATCCACTGAGGGGCCGGGCCCAGCCAGAGCCTGTGCCACC  2100
 630   E  F  T  E  A  E  I  H  *                                     649
2101  GCCCAGAGACCCAGGCCGCCTCGCTCTCCTTCCTGTGTCCAAAACTGCCTCCGGAGGCAG  2160
2161  GGCCTCCAGGCTGTGCCCGGGGAAAGGCAAGGTCCGGCCCATGCCCCGGCACCTCACCGG  2220
2221  CCCCAGGAGAGGCCCAGCCACCAAAGCCGCCTGCGGACAGCCTGAGTCACCTGCAGAACC  2280
2281  TTCTGGAGCTGCCCTAATGCTGGGCTTGCGGGGCAGGGGCCGGCCCACTCTCAGCCCTGC  2340
2341  CACTGCCGGGCGTGCTCCATGGCAGGCGTGGGTGGGGACCGCAGTGTCAGCTCCGACCTC  2400
2401  CAGGCCTCATCCTAGAGACTCTGTCATCTGCCGATCAAGCAAGGTCCTTCCAGAGGAAAG  2460
2461  AATCCTCTTCGCTGGTGGACTGCCAAAAAGTATTTTGCGACATCTTTTGGTTCTGGAGAG  2520
2521  TGGTGAGCAGCCAAGCGACTGTGTCTGAAACACCGTGCATTTTCAGGGAATGTCCCTAAC  2580
2581  GGGCTGGGGACTCTCTCTGCTGGACTTGGGAGTGGCCTTTGCCCCCAGCACACTGTATTC  2640
2641  TGCGGGACCGCCTCCTTCCTGCCCCTAACAACCACCAAAGTGTTGCTGAAATTGGAGAAA  2700
2701  ACTGGGGAAGGCGCAACCCCTCCCAGGTGCGGGAAGCATCTGGTACCGCCTCGGCCAGTG  2760
2761  CCCCTCAGCCTGGCCACAGTCACCTCTCCTTGGGGAACCCTGGGCAGAAAGGGACAGCCT  2820
2821  GTCCTTAGAGGACCGGAAATTGTCAATATTTGATAAAATGATACCCTTTTCTAC  2874
```

FIG.4 cont.

```
   1  TGCCTCCCCGCCCGCGCACCCGCCCCGAGGCCTGTGCTCCTGCGAAGGGGACGCAGCGAA    60
  61  GCCGGGGCCCGCGCCAGGCCGGCCGGGACGGACGCCGATGCCCGGAGCTGCGACGGCTGC   120
 121  AGAGCGAGCTGCCCTCGGAGGCCGGTGTGAGGAAGATGGCCCAGTCCACCACCACCTCCC   180
 -10                                       M  A  Q  S  T  T  T  S  P    9
 181  CCGATGGGGGCACCACGTTTGAGCACCTCTGGAGCTCTCTGGAACCAGACAGCACCTACT   240
  10   D  G  G  T  T  F  E  H  L  W  S  S  L  E  P  D  S  T  Y  F    29
 241  TCGACCTTCCCCAGTCAAGCCGGGGGAATAATGAGGTGGTGGGTGGCACGGATTCCAGCA   300
  30   D  L  P  Q  S  S  R  G  N  N  E  V  V  G  G  T  D  S  S  M    49
 301  TGGACGTCTTCCACCTAGAGGGCATGACCACATCTGTCATGGCCCAGTTCAATTTGCTGA   360
  50   D  V  F  H  L  E  G  M  T  T  S  V  M  A  Q  F  N  L  L  S    69
 361  GCAGCACCATGGACCAGATGAGCAGCCGCGCTGCCTCGGCCAGCCCGTACACCCCGGAGC   420
  70   S  T  M  D  Q  M  S  S  R  A  A  S  A  S  P  Y  T  P  E  H    89
 421  ACGCCGCCAGCGTGCCCACCCATTCACCCTACGCACAGCCCAGCTCCACCTTCGACACCA   480
  90   A  A  S  V  P  T  H  S  P  Y  A  Q  P  S  S  T  F  D  T  M   109
 481  TGTCGCCCGCGCCTGTCATCCCCTCCAACACCGACTATCCCGGACCCCACCACTTCGAGG   540
 110   S  P  A  P  V  I  P  S  N  T  D  Y  P  G  P  H  H  F  E  V   129
 541  TCACTTTCCAGCAGTCCAGCACGGCCAAGTCAGCCACCTGGACGTACTCCCCACTCTTGA   600
 130   T  F  Q  Q  S  S  T  A  K  S  A  T  W  T  Y  S  P  L  L  K   149
 601  AGAAACTCTACTGCCAGATCGCCAAGACATGCCCCATCCAGATCAAGGTGTCCGCCCCAC   660
 150   K  L  Y  C  Q  I  A  K  T  C  P  I  Q  I  K  V  S  A  P  P   169
 661  CGCCCCCGGGCACCGCCATCCGGGCCATGCCTGTCTACAAGAAGGCGGAGCACGTGACCG   720
 170   P  P  G  T  A  I  R  A  M  P  V  Y  K  K  A  E  H  V  T  D   189
 721  ACATCGTGAAGCGCTGCCCCAACCACGAGCTCGGGAGGGACTTCAACGAAGGACAGTCTG   780
 190   I  V  K  R  C  P  N  H  E  L  G  R  D  F  N  E  G  Q  S  A   209
 781  CCCCAGCCAGCCACCTCATCCGTGTGGAAGGCAATAATCTCTCGCAGTATGTGGACGACC   840
 210   P  A  S  H  L  I  R  V  E  G  N  N  L  S  Q  Y  V  D  D  P   229
 841  CTGTCACCGGCAGGCAGAGCGTCGTGGTGCCCTATGAGCCACCACAGGTGGGGACAGAAT   900
 230   V  T  G  R  Q  S  V  V  V  P  Y  E  P  P  Q  V  G  T  E  F   249
 901  TCACCACCATCCTGTACAACTTCATGTGTAACAGCAGCTGTGTGGGGGGCATGAACCGAC   960
 250   T  T  I  L  Y  N  F  M  C  N  S  S  C  V  G  G  M  N  R  R   269
 961  GGCCCATCCTCATCATCATCACCCTGGAGACGCGGGATGGGCAGGTGCTGGGCCGCCGGT  1020
 270   P  I  L  I  I  I  T  L  E  T  R  D  G  Q  V  L  G  R  R  S   289
1021  CCTTCGAGGGCCGCATCTGCGCCTGTCCTGGCCGCGACCGAAAAGCCGATGAGGACCACT  1080
 290   F  E  G  R  I  C  A  C  P  G  R  D  R  K  A  D  E  D  H  Y   309
1081  ACCGGGAGCAGCAGGCCTTGAATGAGAGCTCCGCCAAGAACGGGGCTGCCAGCAAGCGCG  1140
 310   R  E  Q  Q  A  L  N  E  S  S  A  K  N  G  A  A  S  K  R  A   329
1141  CCTTCAAGCAGAGTCCCCCTGCCGTCCCCGCCCTGGGCCCGGGTGTGAAGAAGCGGCGGC  1200
 330   F  K  Q  S  P  P  A  V  P  A  L  G  P  G  V  K  K  R  R  H   349
1201  ACGGAGACGAGGACACGTACTACCTGCAGGTGCGAGGCCGCGAGAACTTCGAGATCCTGA  1260
 350   G  D  E  D  T  Y  Y  L  Q  V  R  G  R  E  N  F  E  I  L  M   369
1261  TGAAGCTGAAGGAGAGCCTGGAGCTGATGGAGTTGGTGCCGCAGCCGCTGGTAGACTCCT  1320
 370   K  L  K  E  S  L  E  L  M  E  L  V  P  Q  P  L  V  D  S  Y   389
1321  ATCGGCAGCAGCAGCAGCTCCTACAGAGGCCGAGTCACCTACAGCCCCCATCCTACGGGC  1380
 390   R  Q  Q  Q  Q  L  L  Q  R  P  S  H  L  Q  P  P  S  Y  G  P   409
1381  CGGTCCTCTCGCCCATGAACAAGGTGCACGGGGGCGTGAACAAGCTGCCCTCCGTCAACC  1440
 410   V  L  S  P  M  N  K  V  H  G  G  V  N  K  L  P  S  V  N  Q   429
1441  AGCTGGTGGGCCAGCCTCCCCCGCACAGCTCGGCAGCTACACCCAACCTGGGACCTGTGG  1500
 430   L  V  G  Q  P  P  P  H  S  S  A  A  T  P  N  L  G  P  V  G   449
1501  GCTCTGGGATGCTCAACAACCACGGCCACGCAGTGCCAGCCAACAGCGAGATGACCAGCA  1560
 450   S  G  M  L  N  N  H  G  H  A  V  P  A  N  S  E  M  T  S  S   469
1561  GCCACGGCACCCAGTCCATGGTCTCGGGGTCCCACTGCACTCCGCCACCCCCCTACCACG  1620
 470   H  G  T  Q  S  M  V  S  G  S  H  C  T  P  P  P  P  Y  H  A   489
1621  CCGACCCCAGCCTCGTCAGGACCTGGGGGCCCTGAAGATCCCCGAGCAGTATCGCATGAC  1680
 490   D  P  S  L  V  R  T  W  G  P  *                                509
1681  CATCTGGCGGGGCCTGCAGGACCTGAAGCAGGGCCACGACTACGGCGCCGCCGCGCAGCA  1740
1741  GCTGCTCCGCTCCAGCAACGCGGCCGCCATTTCCATCGGCGGCTCCGGGGAGCTGCAGCG  1800
1801  CCAGCGGGTCATGGAGGCCGTGCACTTCCGCGTGCGCCACACCATCACCATCCCCAACCG  1860
1861  CGGCGGCCCCGGCGCCGGCCCCGACGAGTGGGCGGACTTCGGCTTCGACCTGCCCGACTG  1920
1921  CAAGGCCCGCAAGCAGCCCATCAAGGAGGAGTTCACGGAGGCCGAGATCCACTGAGGGGC  1980
1981  CGGGCCCAGCCAGAGCCTGTGCCACCGCCCAGAGACCCAGGCCGCCTCGCTCTC  2034
```

FIG.5

```
   1  GCGAGCTGCCCTCGGAGGCCGGCGTGGGGAAGATGGCCCAGTCCACCGCCACCTCCCCTG    60
  -9                                   M  A  Q  S  T  A  T  S  P  D    10
  61  ATGGGGGCACCACGTTTGAGCACCTCTGGAGCTCTCTGGAACCAGACAGCACCTACTTCG   120
  11   G  G  T  T  F  E  H  L  W  S  S  L  E  P  D  S  T  Y  F  D    30
 121  ACCTTCCCCAGTCAAGCCGGGGGAATAATGAGGTGGTGGGCGGAACGGATTCCAGCATGG   180
  31   L  P  Q  S  S  R  G  N  N  E  V  V  G  G  T  D  S  S  M  D    50
 181  ACGTCTTCCACCTGGAGGGCATGACTACATCTGTCATGGCCCAGTTCAATCTGCTGAGCA   240
  51   V  F  H  L  E  G  M  T  T  S  V  M  A  Q  F  N  L  L  S  S    70
 241  GCACCATGGACCAGATGAGCAGCCGCGCGGCCTCGGCCAGCCCCTACACCCCAGAGCACG   300
  71   T  M  D  Q  M  S  S  R  A  A  S  A  S  P  Y  T  P  E  H  A    90
 301  CCGCCAGCGTGCCCACCCACTCGCCCTACGCACAACCCAGCTCCACCTTCGACACCATGT   360
  91   A  S  V  P  T  H  S  P  Y  A  Q  P  S  S  T  F  D  T  M  S   110
 361  CGCCGGCGCCTGTCATCCCCTCCAACACCGACTACCCCGGACCCCACCACTTTGAGGTCA   420
 111   P  A  P  V  I  P  S  N  T  D  Y  P  G  P  H  H  F  E  V  T   130
 421  CTTTCCAGCAGTCCAGCACGGCCAAGTCAGCCACCTGGACGTACTCCCCGCTCTTGAAGA   480
 131   F  Q  Q  S  S  T  A  K  S  A  T  W  T  Y  S  P  L  L  K  K   150
 481  AACTCTACTGCCAGATCGCCAAGACATGCCCCATCCAGATCAAGGTGTCCACCCCGCCAC   540
 151   L  Y  C  Q  I  A  K  T  C  P  I  Q  I  K  V  S  T  P  P  P   170
 541  CCCCAGGCACTGCCATCCGGGCCATGCCTGTTTACAAGAAAGCGGAGCACGTGACCGACG   600
 171   P  G  T  A  I  R  A  M  P  V  Y  K  K  A  E  H  V  T  D  V   190
 601  TCGTGAAACGCTGCCCCAACCACGAGCTCGGGAGGGACTTCAACGAAGGACAGTCTGCTC   660
 191   V  K  R  C  P  N  H  E  L  G  R  D  F  N  E  G  Q  S  A  P   210
 661  CAGCCAGCCACCTCATCCGCGTGGAAGGCAATAATCTCTCGCAGTATGTGGATGACCCTG   720
 211   A  S  H  L  I  R  V  E  G  N  N  L  S  Q  Y  V  D  D  P  V   230
 721  TCACCGGCAGGCAGAGCGTCGTGGTGCCCTATGAGCCACCACAGGTGGGGACGGAATTCA   780
 231   T  G  R  Q  S  V  V  V  P  Y  E  P  P  Q  V  G  T  E  F  T   250
 781  CCACCATCCTGTACAACTTCATGTGTAACAGCAGCTGTGTAGGGGGCATGAACCGGCGGC   840
 251   T  I  L  Y  N  F  M  C  N  S  S  C  V  G  G  M  N  R  R  P   270
 841  CCATCCTCATCATCATCACCCTGGAGATGCGGGATGGGCAGGTGCTGGGCCGCCGGTCCT   900
 271   I  L  I  I  I  T  L  E  M  R  D  G  Q  V  L  G  R  R  S  F   290
 901  TTGAGGGCCGCATCTGCGCCTGTCCTGGCCGCGACCGAAAAGCTGATGAGGACCACTACC   960
 291   E  G  R  I  C  A  C  P  G  R  D  R  K  A  D  E  D  H  Y  R   310
 961  GGGAGCAGCAGGCCCTGAACGAGAGCTCCGCCAAGAACGGGGCCGCCAGCAAGCGTGCCT  1020
 311   E  Q  Q  A  L  N  E  S  S  A  K  N  G  A  A  S  K  R  A  F   330
1021  TCAAGCAGAGCCCCCCTGCCGTCCCCGCCCTTGGTGCCGGTGTGAAGAAGCGGCGGCATG  1080
 331   K  Q  S  P  P  A  V  P  A  L  G  A  G  V  K  K  R  R  H  G   350
1081  GAGACGAGGACACGTACTACCTTCAGGTGCGAGGCCGGGAGAACTTTGAGATCCTGATGA  1140
 351   D  E  D  T  Y  Y  L  Q  V  R  G  R  E  N  F  E  I  L  M  K   370
1141  AGCTGAAAGAGAGCCTGGAGCTGATGGAGTTGGTGCCGCAGCCACTGGTGGACTCCTATC  1200
 371   L  K  E  S  L  E  L  M  E  L  V  P  Q  P  L  V  D  S  Y  R   390
1201  GGCAGCAGCAGCAGCTCCTACAGAGGCCGAGTCACCTACAGCCCCCGTCCTACGGGCCGG  1260
 391   Q  Q  Q  Q  L  L  Q  R  P  S  H  L  Q  P  P  S  Y  G  P  V   410
1261  TCCTCTCGCCCATGAACAAGGTGCACGGGGGCATGAACAAGCTGCCCTCCGTCAACCAGC  1320
 411   L  S  P  M  N  K  V  H  G  G  M  N  K  L  P  S  V  N  Q  L   430
1321  TGGTGGGCCAGCCTCCCCCGCACAGTTCGGCAGCTACACCCAACCTGGGGCCCGTGGGCC  1380
 431   V  G  Q  P  P  P  H  S  S  A  A  T  P  N  L  G  P  V  G  P   450
1381  CCGGGATGCTCAACAACCATGGCCACGCAGTGCCAGCCAACGGCGAGATGAGCAGCAGCC  1440
 451   G  M  L  N  N  H  G  H  A  V  P  A  N  G  E  M  S  S  S  H   470
```

FIG.6

1441	ACAGCGCCCAGTCCATGGTCTCGGGGTCCCACTGCACTCCGCCACCCCCCTACCACGCCG	1500
471	S A Q S M V S G S H C T P P P P Y H A D	490
1501	ACCCCAGCCTCGTCAGTTTTTTAACAGGATTGGGGTGTCCAAACTGCATCGAGTATTTCA	1560
491	P S L V S F L T G L G C P N C I E Y F T	510
1561	CCTCCCAAGGGTTACAGAGCATTTACCACCTGCAGAACCTGACCATTGAGGACCTGGGGG	1620
511	S Q G L Q S I Y H L Q N L T I E D L G A	530
1621	CCCTGAAGATCCCCGAGCAGTACCGCATGACCATCTGGCGGGGCCTGCAGGACCTGAAGC	1680
531	L K I P E Q Y R M T I W R G L Q D L K Q	550
1681	AGGGCCACGACTACAGCACCGCGCAGCAGCTGCTCCGCTCTAGCAACGCGGCCACCATCT	1740
551	G H D Y S T A Q Q L L R S S N A A T I S	570
1741	CCATCGGCGGCTCAGGGGAACTGCAGCGCCAGCGGGTCATGGAGGCCGTGCACTTCCGCG	1800
571	I G G S G E L Q R Q R V M E A V H F R V	590
1801	TGCGCCACACCATCACCATCCCCAACCGCGGCGGCCCAGGCGGCGGCCCTGACGAGTGGG	1860
591	R H T I T I P N R G G P G G G P D E W A	610
1861	CGGACTTCGGCTTCGACCTGCCCGACTGCAAGGCCCGCAAGCAGCCCATCAAGGAGGAGT	1920
611	D F G F D L P D C K A R K Q P I K E E F	630
1921	TCACGGAGGCCGAGATCCACTGAGGGCCTCGCCTGGCTGCAGCCTGCGCCACCGCCCAGA	1980
631	T E A E I H *	650
1981	GACCCAAGCTGCCTCCCCTCTCCTTCCTGTGTGTCCAAAACTGCCTCAGGAGGCAGGACC	2040
2041	TTCGGGCTGTGCCCGGGGAAAGGCAAGGTCCGGCCCATCCCCAGGCACCTCACAGGCCCC	2100
2101	AGGAAAGGCCCAGCCACCGAAGCCGCCTGTGGACAGCCTGAGTCACCTGCAGAACC	2156

FIG.6 cont.

```
   1  TGATCTCCCTGTGGCCTGCAGGGGACTGAGCCAGGGAGTAGATGCCCTGAGACCCCAAGG    60
  61  GACACCCAAGGAAACCTTGCTGGCTTTGAGAAAGGGATCGTCTCTCTCCTGCCCAAGAGA   120
 121  AGCATGTGTATGGGCCCTGTGTATGAATCCTTGGGGCAGGCCCAGTTCAATTTGCTCAGC   180
   0     M  C  M  G  P  V  Y  E  S  L  G  Q  A  Q  F  N  L  L  S    19
 181  AGTGCCATGGACCAGATGGGCAGCCGTGCGGCCCCGGCGAGCCCCTACACCCCGGAGCAC   240
  20  S  A  M  D  Q  M  G  S  R  A  A  P  A  S  P  Y  T  P  E  H    39
 241  GCCGCCAGCGCGCCCACCCACTCGCCCTACGCGCAGCCCAGCTCCACCTTCGACACCATG   300
  40  A  A  S  A  P  T  H  S  P  Y  A  Q  P  S  S  T  F  D  T  M    59
 301  TCTCCGGCGCCTGTCATCCCTTCCAATACCGACTACCCCGGCCCCCACCACTTCGAGGTC   360
  60  S  P  A  P  V  I  P  S  N  T  D  Y  P  G  P  H  H  F  E  V    79
 361  ACCTTCCAGCAGTCGAGCACTGCCAAGTCGGCCACCTGGACATACTCCCCACTCTTGAAG   420
  80  T  F  Q  Q  S  S  T  A  K  S  A  T  W  T  Y  S  P  L  L  K    99
 421  AAGTTGTACTGTCAGATTGCTAAGACATGCCCCATCCAGATCAAAGTGTCCACACCACCA   480
 100  K  L  Y  C  Q  I  A  K  T  C  P  I  Q  I  K  V  S  T  P  P   119
 481  CCCCCGGGCACGGCCATCCGGGCCATGCCTGTCTACAAGAAGGCAGAGCATGTGACCGAC   540
 120  P  P  G  T  A  I  R  A  M  P  V  Y  K  K  A  E  H  V  T  D   139
 541  ATTGTTAAGCGCTGCCCCAACCACGAGCTTGGAAGGGACTTCAATGAAGGACAGTCTGCC   600
 140  I  V  K  R  C  P  N  H  E  L  G  R  D  F  N  E  G  Q  S  A   159
 601  CCGGCTAGCCACCTCATCCGTGTAGAAGGCAACAACCTCGCCCAGTACGTGGATGACCCT   660
 160  P  A  S  H  L  I  R  V  E  G  N  N  L  A  Q  Y  V  D  D  P   179
 661  GTCACCGGAAGGCAGAGTGTGGTTGTGCCGTATGAACCCCCACAGGTGGGAACAGAATTT   720
 180  V  T  G  R  Q  S  V  V  V  P  Y  E  P  P  Q  V  G  T  E  F   199
 721  ACCACCATCCTGTACAACTTCATGTGTAACAGCAGCTGTGTGGGGGGCATGAATCGGAGG   780
 200  T  T  I  L  Y  N  F  M  C  N  S  S  C  V  G  G  M  N  R  R   219
 781  CCCATCCTTGTCATCATCACCCTGGAGACCCGGGATGGACAGGTCCTGGGCCGCCGGTCT   840
 220  P  I  L  V  I  I  T  L  E  T  R  D  G  Q  V  L  G  R  R  S   239
 841  TTCGAGGGTCGCATCTGTGCCTGTCCTGGCCGTGACCGCAAAGCTGATGAAGACCATTAC   900
 240  F  E  G  R  I  C  A  C  P  G  R  D  R  K  A  D  E  D  H  Y   259
 901  CGGGAGCAACAGGCTCTGAATGAAAGTACCACCAAAAATGGAGCTGCCAGCAAACGTGCA   960
 260  R  E  Q  Q  A  L  N  E  S  T  T  K  N  G  A  A  S  K  R  A   279
 961  TTCAAGCAGAGCCCCCCTGCCATCCCTGCCCTGGGTACCAACGTGAAGAAGAGACGCCAC  1020
 280  F  K  Q  S  P  P  A  I  P  A  L  G  T  N  V  K  K  R  R  H   299
1021  GGGGACGAGGACATGTTCTACATGCACGTGCGAGGCCGGGAGAACTTTGAGATCTTGATG  1080
 300  G  D  E  D  M  F  Y  M  H  V  R  G  R  E  N  F  E  I  L  M   319
1081  AAAGTCAAGGAGAGCCTAGAACTGATGGAGCTTGTGCCCCAGCCTTTGGTTGACTCCTAT  1140
 320  K  V  K  E  S  L  E  L  M  E  L  V  P  Q  P  L  V  D  S  Y   339
1141  CGACAGCAGCAGCAGCAGCAGCTCCTACAGAGGCCGAGTCACCTGCAGCCTCCATCCTAT  1200
 340  R  Q  Q  Q  Q  Q  Q  L  L  Q  R  P  S  H  L  Q  P  P  S  Y   359
1201  GGGCCCGTGCTCTCCCCAATGAACAAGGTACACGGTGGTGTCAACAAACTGCCCTCCGTC  1260
 360  G  P  V  L  S  P  M  N  K  V  H  G  G  V  N  K  L  P  S  V   379
1261  AACCAGCTGGTGGGCCAGCCTCCCCCGCACAGCTCAGCAGCTGGGCCCAACCTGGGGCCC  1320
 380  N  Q  L  V  G  Q  P  P  P  H  S  S  A  A  G  P  N  L  G  P   399
1321  ATGGGCTCCGGGATGCTCAACAGCCACGGCCACAGCATGCCGGCCAATGGTGAGATGAAT  1380
 400  M  G  S  G  M  L  N  S  H  G  H  S  M  P  A  N  G  E  M  N   419
1381  GGAGGCCACAGCTCCCAGACCATGGTTTCGGGATCCCACTGcACCCCGCCACCCCCCTAT  1440
 420  G  G  H  S  S  Q  T  M  V  S  G  S  H  C  T  P  P  P  P  Y   439
1441  CATGcAGACCCCAGCCTCGTCAGTTTTTTGACAGGGTTGGGGTGTCCAAACTGCATCGAG  1500
 440  H  A  D  P  S  L  V  S  F  L  T  G  L  G  C  P  N  C  I  E   459
1501  TGCTTCACTTCCCAAGGGTTGCAGAGCATCTACCACCTGCAGAACCTTACCATCGAGGAC  1560
 460  C  F  T  S  Q  G  L  Q  S  I  Y  H  L  Q  N  L  T  I  E  D   479
1561  CTTGGGGCTCTGAAGGTCCCTGACCAGTACCGTATGACCATCTGGAGGGGCCTACAGGAC  1620
 480  L  G  A  L  K  V  P  D  Q  Y  R  M  T  I  W  R  G  L  Q  D   499
1621  CTGAAGCAGAGCCATGACTGCGGCCAGCAACTGCTACGCTCCAGCAGCAACGCGGCCACC  1680
 500  L  K  Q  S  H  D  C  G  Q  Q  L  L  R  S  S  S  N  A  A  T   519
1681  ATCTCCATCGGCGGCTCTGGCGAGCTGCAGCGGCAGCGGGTCATGGAAGCCGTGCATTTC  1740
 520  I  S  I  G  G  S  G  E  L  Q  R  Q  R  V  M  E  A  V  H  F   539
1741  CGTGTGCGCCACACCATCACAATCCCCAACCGTGGAGGCGCAGGTGCGGTGACAGGTCCC  1800
 540  R  V  R  H  T  I  T  I  P  N  R  G  G  A  G  A  V  T  G  P   559
1801  GACGAGTGGGCGGACTTTGGCTTTGACCTGCCTGACTGCAAGTCCCGTAAGCAGCCCATC  1860
 560  D  E  W  A  D  F  G  F  D  L  P  D  C  K  S  R  K  Q  P  I   579
1861  AAAGAGGAGTTCACAGAGACAGAGAGCCACTGAGGAACGTACCTTCTTCTCCTGTCCTTC  1920
 580  K  E  E  F  T  E  T  E  S  H  *                               599
1921  CTCTGTGAGAAACTGCTCTTGGAAGTGGACCTGTTGGCTGTGCCCACAGAAACCAGCAA  1980
1981  GGACCTTCTGCCGGATGCCATTCCTGAAGGGAAGTCGCTCATGAACTAACTCCCTCTTGG  2040
```

FIG.7

```
  1  TGGTCCCGCTTCGACCAAGACTCCGGCTACCAGCTTGCGGCCCCGCGGAGGAGGAGACC   60
 61  CCGCTGGGGCTAGCTGGGCGACGCGCGCCAAGCGGCGGCGGGAAGGAGGCGGGAGGAGCG  120
121  GGGCCCGAGACCCCGACTCGGGCAGAGCCAGCTGGGGAGGCGGGGCGCGCGTGGGAGCCA  180
181  GGGGCCCGGGTGGCCGGCCCTCCTCCGCCACGGCTGAGTGCCCGCGCTGCCTTCCCGCCG  240
241  GTCCGCCAAGAAAGGCGCTAAGCCTGCGGCAGTCCCCTCGCCGCCGCCTCCCTGCTCCGC  300
301  ACCCTTATAACCCGCCGTCCCGCATCCAGGCGAGGAGGCAACGCTGCAGCCCAGCCCTCG  360
361  CCGACGCCGACGCCCGGCCCGGAGCAGAATGAGCGGCAGCGTTGGGGAGATGGCCCAGAC  420
 -8                              M  S  G  S  V  G  E  M  A  Q  T   11
421  CTCTTCTTCCTCCTCCTCCACCTTCGAGCACCTGTGGAGTTCTCTAGAGCCAGACAGCAC  480
 12   S  S  S  S  S  S  T  F  E  H  L  W  S  S  L  E  P  D  S  T   31
481  CTACTTTGACCTCCCCCAGCCCAGCCAAGGGACTAGCGAGGCATCAGGCAGCGAGGAGTC  540
 32   Y  F  D  L  P  Q  P  S  Q  G  T  S  E  A  S  G  S  E  E  S   51
541  CAACATGGATGTCTTCCACCTGCAAGGCATGGCCCAGTTCAATTTGCTCAGCAGTGCCAT  600
 52   N  M  D  V  F  H  L  Q  G  M  A  Q  F  N  L  L  S  S  A  M   71
601  GGACCAGATGGGCAGCCGTGCGGCCCCGGCGAGCCCCTACACCCCGGAGCACGCCGCCAG  660
 72   D  Q  M  G  S  R  A  A  P  A  S  P  Y  T  P  E  H  A  A  S   91
661  CGCGCCCACCCACTCGCCCTACGCGCAGCCCAGCTCCACCTTCGACACCATGTCTCCGGC  720
 92   A  P  T  H  S  P  Y  A  Q  P  S  S  T  F  D  T  M  S  P  A  111
721  GCCTGTCATCCCTTCCAATACCGACTACCCCGGCCCCC  758
112   P  V  I  P  S  N  T  D  Y  P  G  P     123
```

FIG.8

09/125005


```
_ Name: sr-p70a-cos3     Len:   650  Check: 9661  Weight:  1.00
_ Name: sr-p70b-cos3     Len:   650  Check: 3605  Weight:  1.00
_ Name: sr-p70-ht29      Len:   650  Check:   85  Weight:  1.00
_ Name: sr-p70c-att20    Len:   650  Check: 4072  Weight:  1.00
_ Name: sr-p70a-att20    Len:   650  Check: 4204  Weight:  1.00
_
_//
_
_                 1                                                  50
_ sr-p70a-cos3    .......MAQ STTTSPDGGT TFEHLWSSLE PDSTYFDLPQ SSRGNNEVVG
_ sr-p70b-cos3    .......MAQ STTTSPDGGT TFEHLWSSLE PDSTYFDLPQ SSRGNNEVVG
_   sr-p70-ht29   .......MAQ STATSPDGGT TFEHLWSSLE PDSTYFDLPQ SSRGNNEVVG
_sr-p70c-att20    .......... .......... .......... .......... ..........
_sr-p70a-att20    MSGSVGEMAQ ...TSSSSSS TFEHLWSSLE PDSTYFDLPQ PSQGTSEASG
_
_                 51                                                100
_ sr-p70a-cos3    GTDSSMD.VF HLEGMTTSVM AQFNLLSSTM DQMSSRAASA SPYTPEHAAS
_ sr-p70b-cos3    GTDSSMD.VF HLEGMTTSVM AQFNLLSSTM DQMSSRAASA SPYTPEHAAS
_   sr-p70-ht29   GTDSSMD.VF HLEGMTTSVM AQFNLLSSTM DQMSSRAASA SPYTPEHAAS
_sr-p70c-att20    ...MCMGPVY ..ESLG...Q AQFNLLSSAM DQMGSRAAPA SPYTPEHAAS
_sr-p70a-att20    SEESNMD.VF HLQGM..... AQFNLLSSAM DQMGSRAAPA SPYTPEHAAS
_
_                 101                                               150
_ sr-p70a-cos3    VPTHSPYAQP SSTFDTMSPA PVIPSNTDYP GPHHFEVTFQ QSSTAKSATW
_ sr-p70b-cos3    VPTHSPYAQP SSTFDTMSPA PVIPSNTDYP GPHHFEVTFQ QSSTAKSATW
_   sr-p70-ht29   VPTHSPYAQP SSTFDTMSPA PVIPSNTDYP GPHHFEVTFQ QSSTAKSATW
_sr-p70c-att20    APTHSPYAQP SSTFDTMSPA PVIPSNTDYP GPHHFEVTFQ QSSTAKSATW
_sr-p70a-att20    APTHSPYAQP SSTFDTMSPA PVIPSNTDYP GP........ ..........
_
_                 151                                               200
_ sr-p70a-cos3    TYSPLLKKLY CQIAKTCPIQ IKVSAPPPPG TAIRAMPVYK KAEHVTDIVK
_ sr-p70b-cos3    TYSPLLKKLY CQIAKTCPIQ IKVSAPPPPG TAIRAMPVYK KAEHVTDIVK
_   sr-p70-ht29   TYSPLLKKLY CQIAKTCPIQ IKVSTPPPPG TAIRAMPVYK KAEHVTDVVK
_sr-p70c-att20    TYSPLLKKLY CQIAKTCPIQ IKVSTPPPPG TAIRAMPVYK KAEHVTDIVK
_sr-p70a-att20    .......... .......... .......... .......... ..........
_
_                 201                                               250
_ sr-p70a-cos3    RCPNHELGRD FNEGQSAPAS HLIRVEGNNL SQYVDDPVTG RQSVVVPYEP
_ sr-p70b-cos3    RCPNHELGRD FNEGQSAPAS HLIRVEGNNL SQYVDDPVTG RQSVVVPYEP
_   sr-p70-ht29   RCPNHELGRD FNEGQSAPAS HLIRVEGNNL SQYVDDPVTG RQSVVVPYEP
_sr-p70c-att20    RCPNHELGRD FNEGQSAPAS HLIRVEGNNL AQYVDDPVTG RQSVVVPYEP
_sr-p70a-att20    .......... .......... .......... .......... ..........
_
_                 251                                               300
_ sr-p70a-cos3    PQVGTEFTTI LYNFMCNSSC VGGMNRRPIL IIITLETRDG QVLGRRSFEG
_ sr-p70b-cos3    PQVGTEFTTI LYNFMCNSSC VGGMNRRPIL IIITLETRDG QVLGRRSFEG
_   sr-p70-ht29   PQVGTEFTTI LYNFMCNSSC VGGMNRRPIL IIITLEMRDG QVLGRRSFEG
_sr-p70c-att20    PQVGTEFTTI LYNFMCNSSC VGGMNRRPIL VIITLETRDG QVLGRRSFEG
_sr-p70a-att20    .......... .......... .......... .......... ..........
_
_                 301                                               350
_ sr-p70a-cos3    RICACPGRDR KADEDHYREQ QALNESSAKN GAASKRAFKQ SPPAVPALGP
_ sr-p70b-cos3    RICACPGRDR KADEDHYREQ QALNESSAKN GAASKRAFKQ SPPAVPALGP
_   sr-p70-ht29   RICACPGRDR KADEDHYREQ QALNESSAKN GAASKRAFKQ SPPAVPALGA
_sr-p70c-att20    RICACPGRDR KADEDHYREQ QALNESTTKN GAASKRAFKQ SPPAIPALGT
_sr-p70a-att20    .......... .......... .......... .......... ..........
_
```

...

FIG.9

```
               351                                                400
 sr-p70a-cos3  GVKKRRHGDE DTYYLQVRGR ENFEILMKLK ESLELMELVP QPLVDSYR..
 sr-p70b-cos3  GVKKRRHGDE DTYYLQVRGR ENFEILMKLK ESLELMELVP QPLVDSYR..
  sr-p70-ht29  GVKKRRHGDE DTYYLQVRGR ENFEILMKLK ESLELMELVP QPLVDSYR..
sr-p70c-att20  NVKKRRHGDE DMFYMHVRGR ENFEILMKVK ESLELMELVP QPLVDSYRQQ
sr-p70a-att20  .......... .......... .......... .......... ..........

               401                                                450
 sr-p70a-cos3  QQQQLLQRPS HLQPPSYGPV LSPMNKVHGG VNKLPSVNQL VGQPPPHSSA
 sr-p70b-cos3  QQQQLLQRPS HLQPPSYGPV LSPMNKVHGG VNKLPSVNQL VGQPPPHSSA
  sr-p70-ht29  QQQQLLQRPS HLQPPSYGPV LSPMNKVHGG MNKLPSVNQL VGQPPPHSSA
sr-p70c-att20  QQQQLLQRPS HLQPPSYGPV LSPMNKVHGG VNKLPSVNQL VGQPPPHSSA
sr-p70a-att20  .......... .......... .......... .......... ..........

               451                                                500
 sr-p70a-cos3  ATPNLGPVGS GMLNNHGHAV PANSEMTSSH GTQSMVSGSH CTPPPPYHAD
 sr-p70b-cos3  ATPNLGPVGS GMLNNHGHAV PANSEMTSSH GTQSMVSGSH CTPPPPYHAD
  sr-p70-ht29  ATPNLGPVGP GMLNNHGHAV PANGEMSSSH SAQSMVSGSH CTPPPPYHAD
sr-p70c-att20  AGPNLGPMGS GMLNSHGHSM PANGEMNGGH SSQTMVSGSH CTPPPPYHAD
sr-p70a-att20  .......... .......... .......... .......... ..........

               501                                                550
 sr-p70a-cos3  PSLVSFLTGL GCPNCIEYFT SQGLQSIYHL QNLTIEDLGA LKIPEQYRMT
 sr-p70b-cos3  PSLVR..T.W G.P....... .......... .......... ..........
  sr-p70-ht29  PSLVSFLTGL GCPNCIEYFT SQGLQSIYHL QNLTIEDLGA LKIPEQYRMT
sr-p70c-att20  PSLVSFLTGL GCPNCIECFT SQGLQSIYHL QNLTIEDLGA LKVPDQYRMT
sr-p70a-att20  .......... .......... .......... .......... ..........

               551                                                600
 sr-p70a-cos3  IWRGLQDLKQ GHDYGAAAQQ LLR.SSNAAA ISIGGSGELQ RQRVMEAVHF
 sr-p70b-cos3  .......... .......... .......... .......... ..........
  sr-p70-ht29  IWRGLQDLKQ GHDYS.TAQQ LLR.SSNAAT ISIGGSGELQ RQRVMEAVHF
sr-p70c-att20  IWRGLQDLKQ SHDCG...QQ LLRSSSNAAT ISIGGSGELQ RQRVMEAVHF
sr-p70a-att20  .......... .......... .......... .......... ..........

               601                                                650
 sr-p70a-cos3  RVRHTITIPN RGGPGA..GP DEWADFGFDL PDCKARKQPI KEEFTEAEIH
 sr-p70b-cos3  .......... .......... .......... .......... ..........
  sr-p70-ht29  RVRHTITIPN RGGPGG..GP DEWADFGFDL PDCKARKQPI KEEFTEAEIH
sr-p70c-att20  RVRHTITIPN RGGAGAVTGP DEWADFGFDL PDCKSRKQPI KEEFTETESH
sr-p70a-att20  .......... .......... .......... .......... ..........
```

FIG.9 cont.

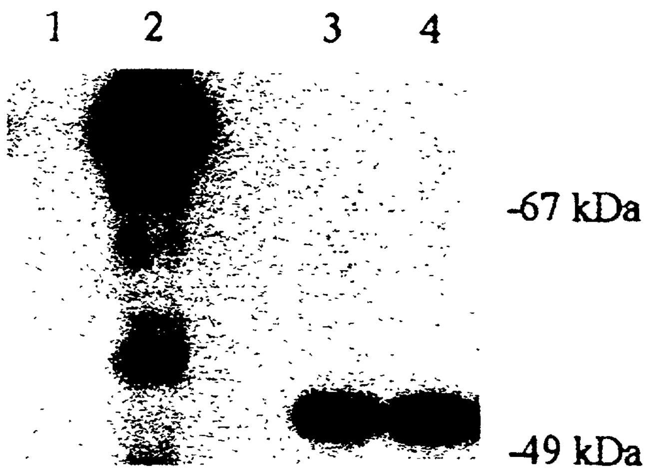

FIG.10a

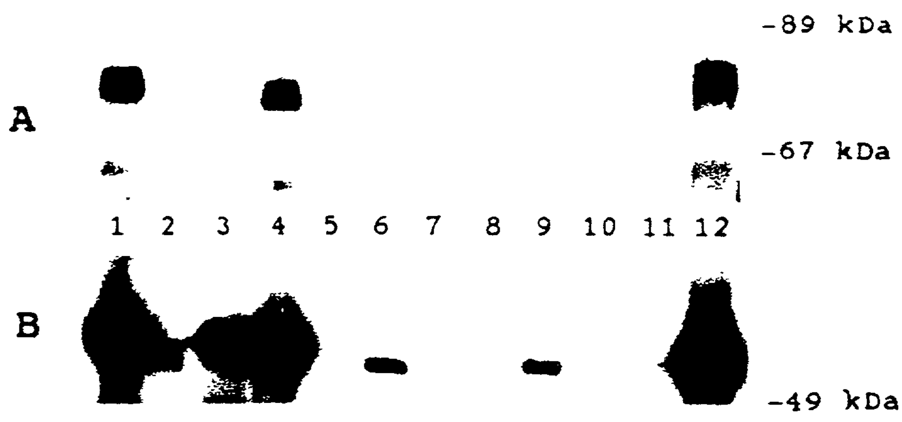

FIG.10b

FIG.11

```
  1 MAQS..TATSPDGGTTFEHLWSSLEPDSTYFDLPQSSRGNNEVVGGTDSSMD  50
  1 MEEPQSDPSVEPPLSQETFSDLWKLLPE.............NNVLSPLPSQAMD  41

 51 VFHLEGMTTSVMAQFNLLSSTMDQMSSRAASASPYTPEHAASVPTHSPYA 100
 42 DLML...SPDDIEQWFTEDPGPDEAPRMPEAAPPVAPAPAAPTPA.APAP  87

101 QPSSTFDTMSPAPVIPSNTDYPGPHHFEVTFQQSSTAKSATWTYSPLLKK 150
 88 APSWPL.....SSSVPSQKTYQGSYGFRLGFLHSGTAKSVTCTYSPALNK 132

151 LYCQIAKTCPIQIKVSTPPPPGTAIRAMPVYKKAEHVTDVVKRCPNHELG 200
133 MFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQSQHMTEVVRRCPHHE.. 180

201 RDFNEGQSAPASHLIRVEGNNLSQYVDDPVTGRQSVVVPYEPPQVGTEFT 250
181 RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTFRHSVVVPYEPPEVGSDCT 230

251 TILYNFMCNSSCVGGMNRRPILIIITLEMRDGQVLGRRSFEGRICACPGR 300
231 TIHYNYMCNSSCMGGMNRRPILTIITLEDSSGNLLGRNSFEVRVCACPGR 280

301 DRKADEDHYREQQALNESSAKNGAASKRAFKQSPPAVPALGAGVKKRRHG 350
281 DRRTEEENLRKKGEPHHELP..PGSTKRALPNNTSSSPQ.....PKKKPL 323

351 DEDTYYLQVRGRENFEILMKLKESLELMELVPQPLVDSYRQQQQLLQRPS 400
324 DGEYFTLQIRGRERFEMFRELNEALELKDAQAGKEPGGSRAHSSHLKSKK 373

401 HLQPPSYGPVLSPMNKVHGGMNKLPSVNQLVGQPPPHSSAATPNLGPVGP 450
374 GQSTSRHKKLMFKTEGPDSD                               393

451 GMLNNHGHAVPANGEMSSSHSAQSMVSGSHCTPPPPYHADPSLVSFLTGL 500

501 GCPNCIEYFTSQGLQSIYHLQNLTIEDLGALKIPEQYRMTIWRGLQDLKQ 550

551 GHDYSTAQQLLRSSNAATISIGGSGELQRQRVMEAVHFRVRHTITIPNRG 600

601 GPGGGPDEWADFGFDLPDCKARKQPIKEEFTEAEIH               636
```

FIG.12

```
                    1  CACCTACTCC AGGGATGCCC CAGGCAGGCC CACTTGCCTG CCGCCCCCAC  INTRON1
                   51  CGAGGCTGTC ACAGGAGGAC AGAGCACGAG TTCCCAGGGT GCTCAGGTGT
CCTCGG  -STY1     101  CATTCCTTCC TTCCTGCAGA GCGAGCTGCC CTCGGAGGCC GGCGTGGGGA  EXON2
CCTTGG  +STY1                                 A          T
                  151  AGATGGCCCA GTCCACCGCC ACCTCCCCTG ATGGGGGCAC CACGTTTGAG
                  201  CACCTCTGGA GCTCTCTGTG AGTGCGCTTG GCTGGCCAGA GCTGGGGGCC
                  251  CCCCTGGGAG GCACTCTGGG CTAGCCTCAG CCACCTTCGC TGGGCTAACT
                  301  GGGCCAGAGC AGGAGGGGTG GCCCCGGGAG GACTCTGGGC TAGCCCCAGC
                  351  CACCCTCACT GAGACTTTGG GCTAAACTTG GCAACCCTCA CTGGGATTCT
                  401  GGGCTAGCCT CGACCACCCT TGCTGCACTA ACTGGACCAG AGCAGGAGAG
                  451  GTGGCTCCAC ACTAGTCTTG GGCTAGCCTT AGCCACCCTC ATCAGCTTGG
                  501  GGACAGGGCG GGTCGGAGGG GCAGGGAAGA GGGACTGCTG CCCTAGGCCT  INTRON2
                  551  TCCCTGGGGA TGCAGGACCA AAATTCAGAC TCTTTTCTCT GGCCAGCTCT
                  601  GGAGAGGGCC CATGGCCAGC AGAGGCCCAG AATAACAGAG CCCATGACTG
                  651  GCTCTGCCTC TCTGGCACTC ACAGCAGCCC TGGAATGGCA GGTGGAGGAC
                  701  AGAGATGGGA TGAGAGGGAA TGGGAAGGGC AGGAGACGTA GGCCTCACCA
                  751  GGAGTCTCAG GCTAGCCTTG AGCTCTGGGC CTGGGAGGTA TTGGGGTGAC
                  801  ACCCAAACTG GGGACTGACG CTTCTATTTT CCTCTCCCTG CCCCAGGGAA  EXON3
                  851  CCAGACAGCA CCTACTTCGA CCTTCCCCAG TCAAGCCGG...
```

FIG.13

```
sr-p70d-imr32                    CG ACCTTCCCCA GTCAAGCCGG GGGAATAATG 32
 sr-p70a-ht29                    CG ACCTTCCCCA GTCAAGCCGG GGGAATAATG 150

              AGGTGGTGGG CGGAACGGAT TCCAGCATGG ACGTCTTCCA CCTGGAGGGC 82
              AGGTGGTGGG CGGAACGGAT TCCAGCATGG ACGTCTTCCA CCTGGAGGGC 200

              ATGACTACAT CTGTCATGCA TCCTCGGCTC CTGCCTCACT AGCTGCGGAG 132
              ATGACTACAT CTGTCAT... .......... .......... .......... 217

              CCTCTCCCGC TCGGTCCACG CTGCCGGGCG GCCACGACCG TGACCCTTCC 182
              .......... .......... .......... .......... ..........

              CCTCGGGCCG CCCAGATCCA TGCCTCGTCC CACGGGACAC CAGTTCCCTG 232
              .. ....... ......... . ......... .......... ..........

              GCGTGTGCAG ACCCCCCGGC GCCTACCATG CTGTACGTCG GTGACCCCGC 282
              .......... .......... .......... .......... ..........

              ACGGCACCTC GCCACGGCCC AGTTCAATCT GCTGAGCAGC ACCATGGACC 332
              .......... .....GGCCC AGTTCAATCT GCTGAGCAGC ACCATGGACC 252

              AGATGAGCAG CCGCGCGGCC TCGGCCAGCC CCTACACCCC AGAGCACGCC 382
              AGATGAGCAG CCGCGCGGCC TCGGCCAGCC CCTACACCCC AGAGCACGCC 302

              GCCAGCGTGC CCACCCACTC GCCCTACGCA CAACCCAGCT CCACCTTCGA 432
              GCCAGCGTGC CCACCCAcTC GCCCTACGCA CAACCCAGCT CCACCTTCGA 352

              CACCATGTCG CCGGCGCCTG TCATCCCCTC CAACACCGAC TACCCCGGAC 482
              CACCATGTCG CCGGCGCCTG TCATCCCCTC CAACACCGAC TACCCCGGAC 402

              CCCACCACTT TGAGGTCACT TTCCAGCAGT CCAGCACGGC CAAGTCAGCC 532
              CCCACCACTT TGAGGTCACT TTCCAGCAGT CCAGCACGGC CAAGTCAGCC 452

              ACCTGGACGT ACTCCCCGCT CTTGAAG
              ACCTGGACGT ACTCCCCGCT CTTGAAG
```

FIG. 14

```
sr-p70a TAACGCCCGCGGCCGCCTACTCCCCGCGGCGCCTCCCCTCCCCGCGCCCA  50
sr-p70f --------------------------------------------------   0
sr-p70d --------------------------------------------------   0
sr-p70e --------------------------------------------------   0
sr-p70b --------------------------------------------------   0

sr-p70a TATAACCCGCCTAGGGGCCGGGCAGCCCGCCCTGCCTCCCCGCCCGCGCA 100
sr-p70f --------------------------------------------------   0
sr-p70d --------------------------------------------------   0
sr-p70e --------------------------------------------------   0
sr-p70b --------------------------------------------------   0

sr-p70a CCCGCCCGGAGGCTCGCGCGCCCGCGAAGGGGACGCAGCGAAACCGGGGC 150
sr-p70f --------------------------------------------------   0
sr-p70d --------------------------------------------------   0
sr-p70e --------------------------------------------------   0
sr-p70b --------------------------------------------------   0

sr-p70a CCGCGCCAGGCCAGCCGGGACGGACGCCGATGCCCGGGGCTGCGACGGCT 200
sr-p70f ------------------------------TGCCCGGGGCTGCGACGGCT  20
sr-p70d --------------------------------------------------   0
sr-p70e --------------------------------------------------   0
sr-p70b --------------------------------------------------   0

sr-p70a GCAGAGCGAGCTGCCCTCGGAGGCCGGCGTGGGGAAGATGGCCCAGTCCA 250
sr-p70f GCAG----------------------------------------------  24
sr-p70d --------------------------------------------------   0
sr-p70e --------------------------------------------------   0
sr-p70b -------------------------------------ATGGCCCAGTCCA  13
```

FIG. 15

```
sr-p70a CCGCCACCTCCCCTGATGGGGGCACCACGTTTGAGCACCTCTGGAGCTCT 300
sr-p70f -------------------------------------------------- 24
sr-p70d -------------------------------------------------- 0
sr-p70e -------------------------------------------------- 0
sr-p70b CCGCCACCTCCCCTGATGGGGGCACCACGTTTGAGCACCTCTGGAGCTCT 63

sr-p70a CTGGAACCAGACAGCACCTACTTCGACCTTCCCCAGTCAAGCCGGGGGAA 350
sr-p70f --GGAACCAGACAGCACCTACTTCGACCTTCCCCAGTCAAGCCGGGGGAA 72
sr-p70d -------------------------------------------------- 0
sr-p70e -------------------------------------------------- 0
sr-p70b CTGGAACCAGACAGCACCTACTTCGACCTTCCCCAGTCAAGCCGGGGGAA 113

sr-p70a TAATGAGGTGGTGGGCGGAACGGATTCCAGCATGGACGTCTTCCACCTGG 400
sr-p70f TAATGAGGTGGTGGGCGGAACGGATTCCAGCATGGACGTCTTCCACCTGG 122
sr-p70d --------ATGCTGTACGTCGGTGACCCCGCACGGCACCTC--------- 33
sr-p70e --------ATGCTGTACGTCGGTGACCCCGCACGGCACCTC--------- 33
sr-p70b TAATGAGGTGGTGGGCGGAACGGATTCCAGCATGGACGTCTTCCACCTGG 163

sr-p70a AGGGCATGACTACATCTGTCATGGCCCAGTTCAATCTGCTGAGCAGCACC 450
sr-p70f AGGGCATGACTACATCTGTCATGGCCCAGTTCAATCTGCTGAGCAGCACC 172
sr-p70d -----------------GCCACGGCCCAGTTCAATCTGCTGAGCAGCACC 66
sr-p70e -----------------GCCACGGCCCAGTTCAATCTGCTGAGCAGCACC 66
sr-p70b AGGGCATGACTACATCTGTCATGGCCCAGTTCAATCTGCTGAGCAGCACC 213

sr-p70a ATGGACCAGATGAGCAGCCGCGCGGCCTCGGCCAGCCCCTACACCCCAGA 500
sr-p70f ATGGACCAGATGAGCAGCCGCGCGGCCTCGGCCAGCCCCTACACCCCAGA 222
sr-p70d ATGGACCAGATGAGCAGCCGCGCGGCCTCGGCCAGCCCCTACACCCCAGA 116
sr-p70e ATGGACCAGATGAGCAGCCGCGCGGCCTCGGCCAGCCCCTACACCCCAGA 116
sr-p70b ATGGACCAGATGAGCAGCCGCGCGGCCTCGGCCAGCCCCTACACCCCAGA 263
```

FIG.15 cont.

```
sr-p70a  GCACGCCGCCAGCGTGCCCACCCACTCGCCCTACGCACAACCCAGCTCCA  550
sr-p70f  GCACGCCGCCAGCGTGCCCACCCACTCGCCCTACGCACAACCCAGCTCCA  272
sr-p70d  GCACGCCGCCAGCGTGCCCACCCACTCGCCCTACGCACAACCCAGCTCCA  166
sr-p70e  GCACGCCGCCAGCGTGCCCACCCACTCGCCCTACGCACAACCCAGCTCCA  166
sr-p70b  GCACGCCGCCAGCGTGCCCACCCACTCGCCCTACGCACAACCCAGCTCCA  313

sr-p70a  CCTTCGACACCATGTCGCCGGCGCCTGTCATCCCCTCCAACACCGACTAC  600
sr-p70f  CCTTCGACACCATGTCGCCGGCGCCTGTCATCCCCTCCAACACCGACTAC  322
sr-p70d  CCTTCGACACCATGTCGCCGGCGCCTGTCATCCCCTCCAACACCGACTAC  216
sr-p70e  CCTTCGACACCATGTCGCCGGCGCCTGTCATCCCCTCCAACACCGACTAC  216
sr-p70b  CCTTCGACACCATGTCGCCGGCGCCTGTCATCCCCTCCAACACCGACTAC  363

sr-p70a  CCCGGACCCCACCACTTTGAGGTCACTTTCCAGCAGTCCAGCACGGCCAA  650
sr-p70f  CCCGGACCCCACCACTTTGAGGTCACTTTCCAGCAGTCCAGCACGGCCAA  372
sr-p70d  CCCGGACCCCACCACTTTGAGGTCACTTTCCAGCAGTCCAGCACGGCCAA  266
sr-p70e  CCCGGACCCCACCACTTTGAGGTCACTTTCCAGCAGTCCAGCACGGCCAA  266
sr-p70b  CCCGGACCCCACCACTTTGAGGTCACTTTCCAGCAGTCCAGCACGGCCAA  413

sr-p70a  GTCAGCCACCTGGACGTACTCCCCGCTCTTGAAGAAACTCTACTGCCAGA  700
sr-p70f  GTCAGCCACCTGGACGTACTCCCCGCTCTTGAAGAAACTCTACTGCCAGA  422
sr-p70d  GTCAGCCACCTGGACGTACTCCCCGCTCTTGAAGAAACTCTACTGCCAGA  316
sr-p70e  GTCAGCCACCTGGACGTACTCCCCGCTCTTGAAGAAACTCTACTGCCAGA  316
sr-p70b  GTCAGCCACCTGGACGTACTCCCCGCTCTTGAAGAAACTCTACTGCCAGA  463

sr-p70a  TCGCCAAGACATGCCCCATCCAGATCAAGGTGTCCACCCCGCCACCCCCA  750
sr-p70f  TCGCCAAGACATGCCCCATCCAGATCAAGGTGTCCACCCCGCCACCCCCA  472
sr-p70d  TCGCCAAGACATGCCCCATCCAGATCAAGGTGTCCACCCCGCCACCCCCA  366
sr-p70e  TCGCCAAGACATGCCCCATCCAGATCAAGGTGTCCACCCCGCCACCCCCA  366
sr-p70b  TCGCCAAGACATGCCCCATCCAGATCAAGGTGTCCACCCCGCCACCCCCA  513
```

FIG.15 cont.

```
sr-p70a  GGCACTGCCATCCGGGCCATGCCTGTTTACAAGAAAGCGGAGCACGTGAC   800
sr-p70f  GGCACTGCCATCCGGGCCATGCCTGTTTACAAGAAAGCGGAGCACGTGAC   522
sr-p70d  GGCACTGCCATCCGGGCCATGCCTGTTTACAAGAAAGCGGAGCACGTGAC   416
sr-p70e  GGCACTGCCATCCGGGCCATGCCTGTTTACAAGAAAGCGGAGCACGTGAC   416
sr-p70b  GGCACTGCCATCCGGGCCATGCCTGTTTACAAGAAAGCGGAGCACGTGAC   563

sr-p70a  CGACGTCGTGAAACGCTGCCCCAACCACGAGCTCGGGAGGGACTTCAACG   850
sr-p70f  CGACGTCGTGAAACGCTGCCCCAACCACGAGCTCGGGAGGGACTTCAACG   572
sr-p70d  CGACGTCGTGAAACGCTGCCCCAACCACGAGCTCGGGAGGGACTTCAACG   466
sr-p70e  CGACGTCGTGAAACGCTGCCCCAACCACGAGCTCGGGAGGGACTTCAACG   466
sr-p70b  CGACGTCGTGAAACGCTGCCCCAACCACGAGCTCGGGAGGGACTTCAACG   613

sr-p70a  AAGGACAGTCTGCTCCAGCCAGCCACCTCATCCGCGTGGAAGGCAATAAT   900
sr-p70f  AAGGACAGTCTGCTCCAGCCAGCCACCTCATCCGCGTGGAAGGCAATAAT   622
sr-p70d  AAGGACAGTCTGCTCCAGCCAGCCACCTCATCCGCGTGGAAGGCAATAAT   516
sr-p70e  AAGGACAGTCTGCTCCAGCCAGCCACCTCATCCGCGTGGAAGGCAATAAT   516
sr-p70b  AAGGACAGTCTGCTCCAGCCAGCCACCTCATCCGCGTGGAAGGCAATAAT   663

sr-p70a  CTCTCGCAGTATGTGGATGACCCTGTCACCGGCAGGCAGAGCGTCGTGGT   950
sr-p70f  CTCTCGCAGTATGTGGATGACCCTGTCACCGGCAGGCAGAGCGTCGTGGT   672
sr-p70d  CTCTCGCAGTATGTGGATGACCCTGTCACCGGCAGGCAGAGCGTCGTGGT   566
sr-p70e  CTCTCGCAGTATGTGGATGACCCTGTCACCGGCAGGCAGAGCGTCGTGGT   566
sr-p70b  CTCTCGCAGTATGTGGATGACCCTGTCACCGGCAGGCAGAGCGTCGTGGT   713

sr-p70a  GCCCTATGAGCCACCACAGGTGGGGACGGAATTCACCACCATCCTGTACA  1000
sr-p70f  GCCCTATGAGCCACCACAGGTGGGGACGGAATTCACCACCATCCTGTACA   722
sr-p70d  GCCCTATGAGCCACCACAGGTGGGGACGGAATTCACCACCATCCTGTACA   616
sr-p70e  GCCCTATGAGCCACCACAGGTGGGGACGGAATTCACCACCATCCTGTACA   616
sr-p70b  GCCCTATGAGCCACCACAGGTGGGGACGGAATTCACCACCATCCTGTACA   763
```

FIG.15 cont.

sr-p70a	A C T T C A T G T G T A A C A G C A G C T G T G T A G G G G G C A T G A A C C G G C G G C C C A T C	1050
sr-p70f	A C T T C A T G T G T A A C A G C A G C T G T G T A G G G G G C A T G A A C C G G C G G C C C A T C	772
sr-p70d	A C T T C A T G T G T A A C A G C A G C T G T G T A G G G G G C A T G A A C C G G C G G C C C A T C	666
sr-p70e	A C T T C A T G T G T A A C A G C A G C T G T G T A G G G G G C A T G A A C C G G C G G C C C A T C	666
sr-p70b	A C T T C A T G T G T A A C A G C A G C T G T G T A G G G G G C A T G A A C C G G C G G C C C A T C	813

sr-p70a	C T C A T C A T C A T C A C C C T G G A G A T G C G G G A T G G G C A G G T G C T G G G C C G C C G	1100
sr-p70f	C T C A T C A T C A T C A C C C T G G A G A T G C G G G A T G G G C A G G T G C T G G G C C G C C G	822
sr-p70d	C T C A T C A T C A T C A C C C T G G A G A T G C G G G A T G G G C A G G T G C T G G G C C G C C G	716
sr-p70e	C T C A T C A T C A T C A C C C T G G A G A T G C G G G A T G G G C A G G T G C T G G G C C G C C G	716
sr-p70b	C T C A T C A T C A T C A C C C T G G A G A T G C G G G A T G G G C A G G T G C T G G G C C G C C G	863

sr-p70a	G T C C T T T G A G G G C C G C A T C T G C G C C T G T C C T G G C C G C G A C C G A A A A G C T G	1150
sr-p70f	G T C C T T T G A G G G C C G C A T C T G C G C C T G T C C T G G C C G C G A C C G A A A A G C T G	872
sr-p70d	G T C C T T T G A G G G C C G C A T C T G C G C C T G T C C T G G C C G C G A C C G A A A A G C T G	766
sr-p70e	G T C C T T T G A G G G C C G C A T C T G C G C C T G T C C T G G C C G C G A C C G A A A A G C T G	766
sr-p70b	G T C C T T T G A G G G C C G C A T C T G C G C C T G T C C T G G C C G C G A C C G A A A A G C T G	913

sr-p70a	A T G A G G A C C A C T A C C G G G A G C A G C A G G C C C T G A A C G A G A G C T C C G C C A A G	1200
sr-p70f	A T G A G G A C C A C T A C C G G G A G C A G C A G G C C C T G A A C G A G A G C T C C G C C A A G	922
sr-p70d	A T G A G G A C C A C T A C C G G G A G C A G C A G G C C C T G A A C G A G A G C T C C G C C A A G	816
sr-p70e	A T G A G G A C C A C T A C C G G G A G C A G C A G G C C C T G A A C G A G A G C T C C G C C A A G	816
sr-p70b	A T G A G G A C C A C T A C C G G G A G C A G C A G G C C C T G A A C G A G A G C T C C G C C A A G	963

sr-p70a	A A C G G G G C C G C C A G C A A G C G T G C C T T C A A G C A G A G C C C C C C T G C C G T C C C	1250
sr-p70f	A A C G G G G C C G C C A G C A A G C G T G C C T T C A A G C A G A G C C C C C C T G C C G T C C C	972
sr-p70d	A A C G G G G C C G C C A G C A A G C G T G C C T T C A A G C A G A G C C C C C C T G C C G T C C C	866
sr-p70e	A A C G G G G C C G C C A G C A A G C G T G C C T T C A A G C A G A G C C C C C C T G C C G T C C C	866
sr-p70b	A A C G G G G C C G C C A G C A A G C G T G C C T T C A A G C A G A G C C C C C C T G C C G T C C C	1013

FIG. 15 cont.

```
sr-p70a  C G C C C T T G G T G C C G G T G T G A A G A A G C G G C G G C A T G G A G A C G A G G A C A C G T  1300
sr-p70f  C G C C C T T G G T G C C G G T G T G A A G A A G C G G C G G C A T G G A G A C G A G G A C A C G T  1022
sr-p70d  C G C C C T T G G T G C C G G T G T G A A G A A G C G G C G G C A T G G A G A C G A G G A C A C G T   916
sr-p70e  C G C C C T T G G T G C C G G T G T G A A G A A G C G G C G G C A T G G A G A C G A G G A C A C G T   916
sr-p70b  C G C C C T T G G T G C C G G T G T G A A G A A G C G G C G G C A T G G A G A C G A G G A C A C G T  1063

sr-p70a  A C T A C C T T C A G G T G C G A G G C C G G G A G A A C T T T G A G A T C C T G A T G A A G C T G  1350
sr-p70f  A C T A C C T T C A G G T G C G A G G C C G G G A G A A C T T T G A G A T C C T G A T G A A G C T G  1072
sr-p70d  A C T A C C T T C A G G T G C G A G G C C G G G A G A A C T T T G A G A T C C T G A T G A A G C T G   966
sr-p70e  A C T A C C T T C A G G T G C G A G G C C G G G A G A A C T T T G A G A T C C T G A T G A A G C T G   966
sr-p70b  A C T A C C T T C A G G T G C G A G G C C G G G A G A A C T T T G A G A T C C T G A T G A A G C T G  1113

sr-p70a  A A A G A G A G C C T G G A G C T G A T G G A G T T G G T G C C G C A G C C A C T G G T G G A C T C  1400
sr-p70f  A A A G A G A G C C T G G A G C T G A T G G A G T T G G T G C C G C A G C C A C T G G T G G A C T C  1122
sr-p70d  A A A G A G A G C C T G G A G C T G A T G G A G T T G G T G C C G C A G C C A C T G G T G G A C T C  1016
sr-p70e  A A A G A G A G C C T G G A G C T G A T G G A G T T G G T G C C G C A G C C A C T G G T G G A C T C  1016
sr-p70b  A A A G A G A G C C T G G A G C T G A T G G A G T T G G T G C C G C A G C C A C T G G T G G A C T C  1163

sr-p70a  C T A T C G G C A G C A G C A G C A G C T C C T A C A G A G G C C G A G T C A C C T A C A G C C C C  1450
sr-p70f  C T A T C G G C A G C A G C A G C A G C T C C T A C A G A G G C C G A G T C A C C T A C A G C C C C  1172
sr-p70d  C T A T C G G C A G C A G C A G C A G C T C C T A C A G A G G C C G A G T C A C C T A C A G C C C C  1066
sr-p70e  C T A T C G G C A G C A G C A G C A G C T C C T A C A G A G G C C - - - - - - - - - - - - - - - - -  1049
sr-p70b  C T A T C G G C A G C A G C A G C A G C T C C T A C A G A G G C C G A G T C A C C T A C A G C C C C  1213

sr-p70a  C G T C C T A C G G G C C G G T C C T C T C G C C C A T G A A C A A G G T G C A C G G G G G C A T G  1500
sr-p70f  C G T C C T A C G G G C C G G T C C T C T C G C C C A T G A A C A A G G T G C A C G G G G G C A T G  1222
sr-p70d  C G T C C T A C G G G C C G G T C C T C T C G C C C A T G A A C A A G G T G C A C G G G G G C A T G  1116
sr-p70e  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  1049
sr-p70b  C G T C C T A C G G G C C G G T C C T C T C G C C C A T G A A C A A G G T G C A C G G G G G C A T G  1263
```

FIG. 15 cont.

```
sr-p70a AACAAGCTGCCCTCCGTCAACCAGCTGGTGGGCCAGCCTCCCCCGCACAG 1550
sr-p70f AACAAGCTGCCCTCCGTCAACCAGCTGGTGGGCCAGCCTCCCCCGCACAG 1272
sr-p70d AACAAGCTGCCCTCCGTCAACCAGCTGGTGGGCCAGCCTCCCCCGCACAG 1166
sr-p70e -------------------------------------------------- 1049
sr-p70b AACAAGCTGCCCTCCGTCAACCAGCTGGTGGGCCAGCCTCCCCCGCACAG 1313

sr-p70a TTCGGCAGCTACACCCAACCTGGGGCCCGTGGGCCCCGGGATGCTCAACA 1600
sr-p70f TTCGGCAGCTACACCCAACCTGGGGCCCGTGGGCCCCGGGATGCTCAACA 1322
sr-p70d TTCGGCAGCTACACCCAACCTGGGGCCCGTGGGCCCCGGGATGCTCAACA 1216
sr-p70e --------------------------------GCCCCGGGATGCTCAACA 1067
sr-p70b TTCGGCAGCTACACCCAACCTGGGGCCCGTGGGCCCCGGGATGCTCAACA 1363

sr-p70a ACCATGGCCACGCAGTGCCAGCCAACGGCGAGATGAGCAGCAGCCACAGC 1650
sr-p70f ACCATGGCCACGCAGTGCCAGCCAACGGCGAGATGAGCAGCAGCCACAGC 1372
sr-p70d ACCATGGCCACGCAGTGCCAGCCAACGGCGAGATGAGCAGCAGCCACAGC 1266
sr-p70e ACCATGGCCACGCAGTGCCAGCCAACGGCGAGATGAGCAGCAGCCACAGC 1117
sr-p70b ACCATGGCCACGCAGTGCCAGCCAACGGCGAGATGAGCAGCAGCCACAGC 1413

sr-p70a GCCCAGTCCATGGTCTCGGGGTCCCACTGCACTCCGCCACCCCCCTACCA 1700
sr-p70f GCCCAGTCCATGGTCTCGGGGTCCCACTGCACTCCGCCACCCCCCTACCA 1422
sr-p70d GCCCAGTCCATGGTCTCGGGGTCCCACTGCACTCCGCCACCCCCCTACCA 1316
sr-p70e GCCCAGTCCATGGTCTCGGGGTCCCACTGCACTCCGCCACCCCCCTACCA 1167
sr-p70b GCCCAGTCCATGGTCTCGGGGTCCCACTGCACTCCGCCACCCCCCTACCA 1463

sr-p70a CGCCGACCCCAGCCTCGTCAGTTTTTTAACAGGATTGGGGTGTCCAAACT 1750
sr-p70f CGCCGACCCCAGCCTCGTCAGTTTTTTAACAGGATTGGGGTGTCCAAACT 1472
sr-p70d CGCCGACCCCAGCCTCGTCAGTTTTTTAACAGGATTGGGGTGTCCAAACT 1366
sr-p70e CGCCGACCCCAGCCTCGTC------------------------------- 1186
sr-p70b CGCCGACCCCAGCCTCGTC------------------------------- 1482
```

FIG. 15 cont.

```
sr-p70a GCATCGAGTATTTCACCTCCCAAGGGTTACAGAGCATTTACCACCTGCAG 1800
sr-p70f GCATCGAGTATTTCACCTCCCAAGGGTTACAGAGCATTTACCACCTGCAG 1522
sr-p70d GCATCGAGTATTTCACCTCCCAAGGGTTACAGAGCATTTACCACCTGCAG 1416
sr-p70e -------------------------------------------------- 1186
sr-p70b -------------------------------------------------- 1482

sr-p70a AACCTGACCATTGAGGACCTGGGGGCCCTGAAGATCCCCGAGCAGTACCG 1850
sr-p70f AACCTGACCATTGAGGACCTGGGGGCCCTGAAGATCCCCGAGCAGTACCG 1572
sr-p70d AACCTGACCATTGAGGACCTGGGGGCCCTGAAGATCCCCGAGCAGTACCG 1466
sr-p70e -------------AGGACCTGGGGGCCCTGAAGATCCCCGAGCAGTACCG 1223
sr-p70b -------------AGGACCTGGGGGCCCTGAAGATCCCCGAGCAGTACCG 1519

sr-p70a CATGACCATCTGGCGGGGCCTGCAGGACCTGAAGCAGGGCCACGACTACA 1900
sr-p70f CATGACCATCTGGCGGGGCCTGCAGGACCTGAAGCAGGGCCACGACTACA 1622
sr-p70d CATGACCATCTGGCGGGGCCTGCAGGACCTGAAGCAGGGCCACGACTACA 1516
sr-p70e CATGACCATCTGGCGGGGCCTGCAGGACCTGAAGCAGGGCCACGACTACA 1273
sr-p70b CATGACCATCTGGCGGGGCCTGCAGGACCTGAAGCAGGGCCACGACTACA 1569

sr-p70a GCACCGCGCAGCAGCTGCTCCGCTCTAGCAACGCGGCCACCATCTCCATC 1950
sr-p70f GCACCGCGCAGCAGCTGCTCCGCTCTAGCAACGCGGCCACCATCTCCATC 1672
sr-p70d GCACCGCGCAGCAGCTGCTCCGCTCTAGCAACGCGGCCACCATCTCCATC 1566
sr-p70e GCACCGCGCAGCAGCTGCTCCGCTCTAGCAACGCGGCCACCATCTCCATC 1323
sr-p70b GCACCGCGCAGCAGCTGCTCCGCTCTAGCAACGCGGCCACCATCTCCATC 1619

sr-p70a GGCGGCTCAGGGGAACTGCAGCGCCAGCGGGTCATGGAGGCCGTGCACTT 2000
sr-p70f GGCGGCTCAGGGGAACTGCAGCGCCAGCGGGTCATGGAGGCCGTGCACTT 1722
sr-p70d GGCGGCTCAGGGGAACTGCAGCGCCAGCGGGTCATGGAGGCCGTGCACTT 1616
sr-p70e GGCGGCTCAGGGGAACTGCAGCGCCAGCGGGTCATGGAGGCCGTGCACTT 1373
sr-p70b GGCGGCTCAGGGGAACTGCAGCGCCAGCGGGTCATGGAGGCCGTGCACTT 1669
```

FIG. 15cont.

```
sr-p70a  CCGCGTGCGCCACACCATCACCATCCCCAACCGCGGCGGCCCAGGCGGCG  2050
sr-p70f  CCGCGTGCGCCACACCATCACCATCCCCAACCGCGGCGGCCCAGGCGGCG  1772
sr-p70d  CCGCGTGCGCCACACCATCACCATCCCCAACCGCGGCGGCCCAGGCGGCG  1666
sr-p70e  CCGCGTGCGCCACACCATCACCATCCCCAACCGCGGCGGCCCAGGCGGCG  1423
sr-p70b  CCGCGTGCGCCACACCATCACCATCCCCAACCGCGGCGGCCCAGGCGGCG  1719

sr-p70a  GCCCTGACGAGTGGGCGGACTTCGGCTTCGACCTGCCCGACTGCAAGGCC  2100
sr-p70f  GCCCTGACGAGTGGGCGGACTTCGGCTTCGACCTGCCCGACTGCAAGGCC  1822
sr-p70d  GCCCTGACGAGTGGGCGGACTTCGGCTTCGACCTGCCCGACTGCAAGGCC  1716
sr-p70e  GCCCTGACGAGTGGGCGGACTTCGGCTTCGACCTGCCCGACTGCAAGGCC  1473
sr-p70b  GCCCTGACGAGTGGGCGGACTTCGGCTTCGACCTGCCCGACTGCAAGGCC  1769

sr-p70a  CGCAAGCAGCCCATCAAGGAGGAGTTCACGGAGGCCGAGATCCACTGAGG  2150
sr-p70f  CGCAAGCAGCCCATCAAGGAGGAGTTCACGGAGGCCGAGATCCACTGA--  1870
sr-p70d  CGCAAGCAGCCCATCAAGGAGGAGTTCACGGAGGCCGAGATCCACTGA--  1764
sr-p70e  CGCAAGCAGCCCATCAAGGAGGAGTTCACGGAGGCCGAGATCCACTGA--  1521
sr-p70b  CGCAAGCAGCCCATCAAGGAGGAGTTCACGGAGGCCGAGATCCACTGA--  1817

sr-p70a  GCCTCGCCTGGCTGCAGCCTGCGCCACCGCCCAGAGACCCAAGCTGCCTC  2200
sr-p70f  --------------------------------------------------  1870
sr-p70d  --------------------------------------------------  1764
sr-p70e  --------------------------------------------------  1521
sr-p70b  --------------------------------------------------  1817

sr-p70a  CCCTCTCCTTCCTGTGTGTCCAAAACTGCCTCAGGAGGCAGGACCTTCGG  2250
sr-p70f  --------------------------------------------------  1870
sr-p70d  --------------------------------------------------  1764
sr-p70e  --------------------------------------------------  1521
sr-p70b  --------------------------------------------------  1817
```

FIG.15 cont.

```
sr-p70a G C T G T G C C C G G G G A A A G G C A A G G T C C G G C C C A T C C C C A G G C A C C T C A C A G  2300
sr-p70f - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  1870
sr-p70d - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  1764
sr-p70e - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  1521
sr-p70b - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  1817

sr-p70a G C C C C A G G A A A G G C C C A G C C A C C G A A G C C G C C T G T G G A C A G C C T G A G T C A  2350
sr-p70f - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  1870
sr-p70d - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  1764
sr-p70e - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  1521
sr-p70b - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  1817

sr-p70a C C T G C A G A A C C                                                                                2361
sr-p70f - - - - - - - - - - -                                                                                1870
sr-p70d - - - - - - - - - - -                                                                                1764
sr-p70e - - - - - - - - - - -                                                                                1521
sr-p70b - - - - - - - - - - -                                                                                1817
```

FIG.15 cont.

```
sr-p70a_  MAQSTATSPDGGTTFEHLWSSLEPDSTYFDLPQSSRGNNEVVGGTDSSMD   50
sr-p70f_  ------------------------------------------------MD    2
sr-p70d_  -------------------------------------------------M    1
sr-p70b_  MAQSTATSPDGGTTFEHLWSSLEPDSTYFDLPQSSRGNNEVVGGTDSSMD   50
sr-p70e_  -------------------------------------------------M    1

sr-p70a_  VFHLEGMTTSVMAQFNLLSSTMDQMSSRAASASPYTPEHAASVPTHSPYA  100
sr-p70f_  VFHLEGMTTSVMAQFNLLSSTMDQMSSRAASASPYTPEHAASVPTHSPYA   52
sr-p70d_  LYVGDPARHLATAQFNLLSSTMDQMSSRAASASPYTPEHAASVPTHSPYA   51
sr-p70b_  VFHLEGMTTSVMAQFNLLSSTMDQMSSRAASASPYTPEHAASVPTHSPYA  100
sr-p70e_  LYVGDPARHLATAQFNLLSSTMDQMSSRAASASPYTPEHAASVPTHSPYA   51

sr-p70a_  QPSSTFDTMSPAPVIPSNTDYPGPHHFEVTFQQSSTAKSATWTYSPLLKK  150
sr-p70f_  QPSSTFDTMSPAPVIPSNTDYPGPHHFEVTFQQSSTAKSATWTYSPLLKK  102
sr-p70d_  QPSSTFDTMSPAPVIPSNTDYPGPHHFEVTFQQSSTAKSATWTYSPLLKK  101
sr-p70b_  QPSSTFDTMSPAPVIPSNTDYPGPHHFEVTFQQSSTAKSATWTYSPLLKK  150
sr-p70e_  QPSSTFDTMSPAPVIPSNTDYPGPHHFEVTFQQSSTAKSATWTYSPLLKK  101

sr-p70a_  LYCQIAKTCPIQIKVSTPPPPGTAIRAMPVYKKAEHVTDVVKRCPNHELG  200
sr-p70f_  LYCQIAKTCPIQIKVSTPPPPGTAIRAMPVYKKAEHVTDVVKRCPNHELG  152
sr-p70d_  LYCQIAKTCPIQIKVSTPPPPGTAIRAMPVYKKAEHVTDVVKRCPNHELG  151
sr-p70b_  LYCQIAKTCPIQIKVSTPPPPGTAIRAMPVYKKAEHVTDVVKRCPNHELG  200
sr-p70e_  LYCQIAKTCPIQIKVSTPPPPGTAIRAMPVYKKAEHVTDVVKRCPNHELG  151

sr-p70a_  RDFNEGQSAPASHLIRVEGNNLSQYVDDPVTGRQSVVVPYEPPQVGTEFT  250
sr-p70f_  RDFNEGQSAPASHLIRVEGNNLSQYVDDPVTGRQSVVVPYEPPQVGTEFT  202
sr-p70d_  RDFNEGQSAPASHLIRVEGNNLSQYVDDPVTGRQSVVVPYEPPQVGTEFT  201
sr-p70b_  RDFNEGQSAPASHLIRVEGNNLSQYVDDPVTGRQSVVVPYEPPQVGTEFT  250
sr-p70e_  RDFNEGQSAPASHLIRVEGNNLSQYVDDPVTGRQSVVVPYEPPQVGTEFT  201
```

FIG. 16

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```
sr-p70a_ TILYNFMCNSSCVGGMNRRPILIIITLEMRDGQVLGRRSFEGRICACPGR 300
sr-p70f_ TILYNFMCNSSCVGGMNRRPILIIITLEMRDGQVLGRRSFEGRICACPGR 252
sr-p70d_ TILYNFMCNSSCVGGMNRRPILIIITLEMRDGQVLGRRSFEGRICACPGR 251
sr-p70b_ TILYNFMCNSSCVGGMNRRPILIIITLEMRDGQVLGRRSFEGRICACPGR 300
sr-p70e_ TILYNFMCNSSCVGGMNRRPILIIITLEMRDGQVLGRRSFEGRICACPGR 251

sr-p70a_ DRKADEDHYREQQALNESSAKNGAASKRAFKQSPPAVPALGAGVKKRRHG 350
sr-p70f_ DRKADEDHYREQQALNESSAKNGAASKRAFKQSPPAVPALGAGVKKRRHG 302
sr-p70d_ DRKADEDHYREQQALNESSAKNGAASKRAFKQSPPAVPALGAGVKKRRHG 301
sr-p70b_ DRKADEDHYREQQALNESSAKNGAASKRAFKQSPPAVPALGAGVKKRRHG 350
sr-p70e_ DRKADEDHYREQQALNESSAKNGAASKRAFKQSPPAVPALGAGVKKRRHG 301

sr-p70a_ DEDTYYLQVRGRENFEILMKLKESLELMELVPQPLVDSYRQQQQLLQRPS 400
sr-p70f_ DEDTYYLQVRGRENFEILMKLKESLELMELVPQPLVDSYRQQQQLLQRPS 352
sr-p70d_ DEDTYYLQVRGRENFEILMKLKESLELMELVPQPLVDSYRQQQQLLQRPS 351
sr-p70b_ DEDTYYLQVRGRENFEILMKLKESLELMELVPQPLVDSYRQQQQLLQRPS 400
sr-p70e_ DEDTYYLQVRGRENFEILMKLKESLELMELVPQPLVDSYRQQQQLLQRPP 351

sr-p70a_ HLQPPSYGPVLSPMNKVHGGMNKLPSVNQLVGQPPPHSSAATPNLGPVGP 450
sr-p70f_ HLQPPSYGPVLSPMNKVHGGMNKLPSVNQLVGQPPPHSSAATPNLGPVGP 402
sr-p70d_ HLQPPSYGPVLSPMNKVHGGMNKLPSVNQLVGQPPPHSSAATPNLGPVGP 401
sr-p70b_ HLQPPSYGPVLSPMNKVHGGMNKLPSVNQLVGQPPPHSSAATPNLGPVGP 450
sr-p70e_ RDAQQPWP-----------------RSASQRRDEQQPQRPV--------- 375

sr-p70a_ GMLNNHGHAVPANGEMSSSHSAQSMVSGSHCTPPPPYHADPSLVSFLTGL 500
sr-p70f_ GMLNNHGHAVPANGEMSSSHSAQSMVSGSHCTPPPPYHADPSLVSFLTGL 452
sr-p70d_ GMLNNHGHAVPANGEMSSSHSAQSMVSGSHCTPPPPYHADPSLVSFLTGL 451
sr-p70b_ GMLNNHGHAVPANGEMSSSHSAQSMVSGSHCTPPPPYHADPSLVRTWGP- 499
sr-p70e_ -----HGLGVPL------------------HSATPLPRRPQPR------- 395
```

FIG. 16 cont.

```
sr-p70a_ G C P N C I E Y F T S Q G L Q S I Y H L Q N L T I E D L G A L K I P E Q Y R M T I W R G L Q D L K Q  550
sr-p70f_ G C P N C I E Y F T S Q G L Q S I Y H L Q N L T I E D L G A L K I P E Q Y R M T I W R G L Q D L K Q  502
sr-p70d_ G C P N C I E Y F T S Q G L Q S I Y H L Q N L T I E D L G A L K I P E Q Y R M T I W R G L Q D L K Q  501
sr-p70b_ - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  499
sr-p70e_ - - - - - - - - - - - - - - - - - - - - - - - - - Q D L G A L K I P E Q Y R M T I W R G L Q D L K Q  420

sr-p70a_ G H D Y S T A Q Q L L R S S N A A T I S I G G S G E L Q R Q R V M E A V H F R V R H T I T I P N R G  600
sr-p70f_ G H D Y S T A Q Q L L R S S N A A T I S I G G S G E L Q R Q R V M E A V H F R V R H T I T I P N R G  552
sr-p70d_ G H D Y S T A Q Q L L R S S N A A T I S I G G S G E L Q R Q R V M E A V H F R V R H T I T I P N R G  551
sr-p70b_ - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  499
sr-p70e_ G H D Y S T A Q Q L L R S S N A A T I S I G G S G E L Q R Q R V M E A V H F R V R H T I T I P N R G  470

sr-p70a_ G P G G G P D E W A D F G F D L P D C K A R K Q P I K E E F T E A E I H  636
sr-p70f_ G P G G G P D E W A D F G F D L P D C K A R K Q P I K E E F T E A E I H  588
sr-p70d_ G P G G G P D E W A D F G F D L P D C K A R K Q P I K E E F T E A E I H  587
sr-p70b_ - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  499
sr-p70e_ G P G G G P D E W A D F G F D L P D C K A R K Q P I K E E F T E A E I H  506
```

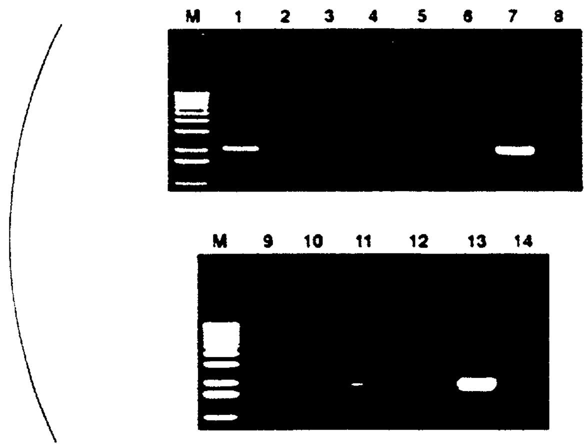
FIG.16 cont.

```
  1  TAACGCCCGCGGCCGCCTACTCCCCGCGGCGCCTCCCCTCCCCGCGCCCATATAACCCGC   60
 61  CTAGGGGCCGGGCAGCCCGCCCTGCCTCCCCGCCCGCGCACCCGCCCGGAGGCTCGCGCG  120
121  CCCGCGAAGGGGACGCAGCGAAACCGGGGCCCGCGCCAGGCCAGCCGGGACGGACGCCGA  180
181  TGCCCGGGGCTGCGACGGCTGCAGAGCAAGCTGCCCTTGGAGGCCGGCGTGGGGAAGATG  240
                                                           M    1
241  GCCCAGTCCACCGCCACCTCCCCTGATGGGGGCACCACGTTTGAGCACCTCTGGAGCTCT  300
  2  A  Q  S  T  A  T  S  P  D  G  G  T  T  F  E  H  L  W  S  S    21
301  CTGGAACCAGACAGCACCTACTTCGACCTTCCCCAGTCAAGCCGGGGGAATAATGAGGTG  360
 22  L  E  P  D  S  T  Y  F  D  L  P  Q  S  S  R  G  N  N  E  V    41
361  GTGGGCGGAACGGATTCCAGCATGGACGTCTTCCACCTGGAGGGCATGACtACATCTGTC  420
 42  V  G  G  T  D  S  S  M  D  V  F  H  L  E  G  M  T  T  S  V    61
421  ATGGCCCAGTTCAATCTGCTGAGCAGCACCATGGACCAGATGAGCAGCCGCGCGGCCTCG  480
 62  M  A  Q  F  N  L  L  S  S  T  M  D  Q  M  S  S  R  A  A  S    81
481  GCCAGCCCCTACACCCCAGAGCACGCCGCCAGCGTGCCCACCCACTCGCCCTACGCACAA  540
 82  A  S  P  Y  T  P  E  H  A  A  S  V  P  T  H  S  P  Y  A  Q   101
541  CCCAGCTCCACCTTCGACACCATGTCGCCGGCGCCTGTCATCCCCTCCAACACCGACTAC  600
102  P  S  S  T  F  D  T  M  S  P  A  P  V  I  P  S  N  T  D  Y   121
601  CCCGGACCCCACCACTTTGAGGTCACTTTCCAGCAGTCCAGCACGGCCAAGTCAGCCACC  660
122  P  G  P  H  H  F  E  V  T  F  Q  Q  S  S  T  A  K  S  A  T   141
661  TGGACGTA......
142  W  T     .  .
```

FIG.17

no/125005

FIG. 18



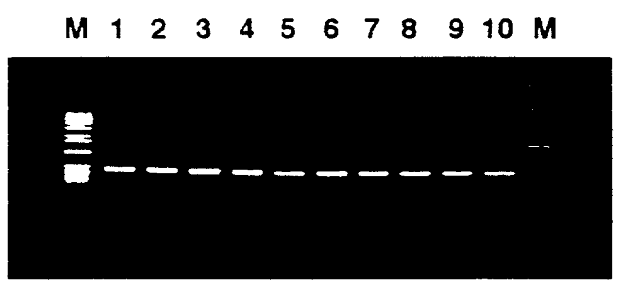


FIG. 19A

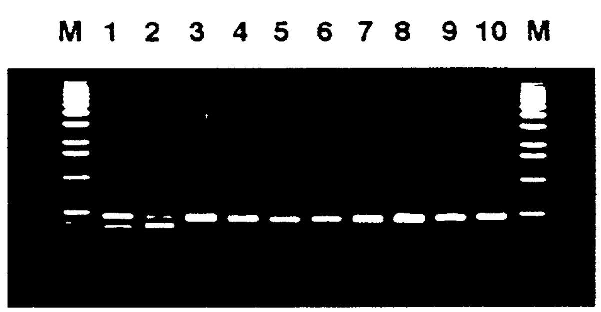


FIG. 19B

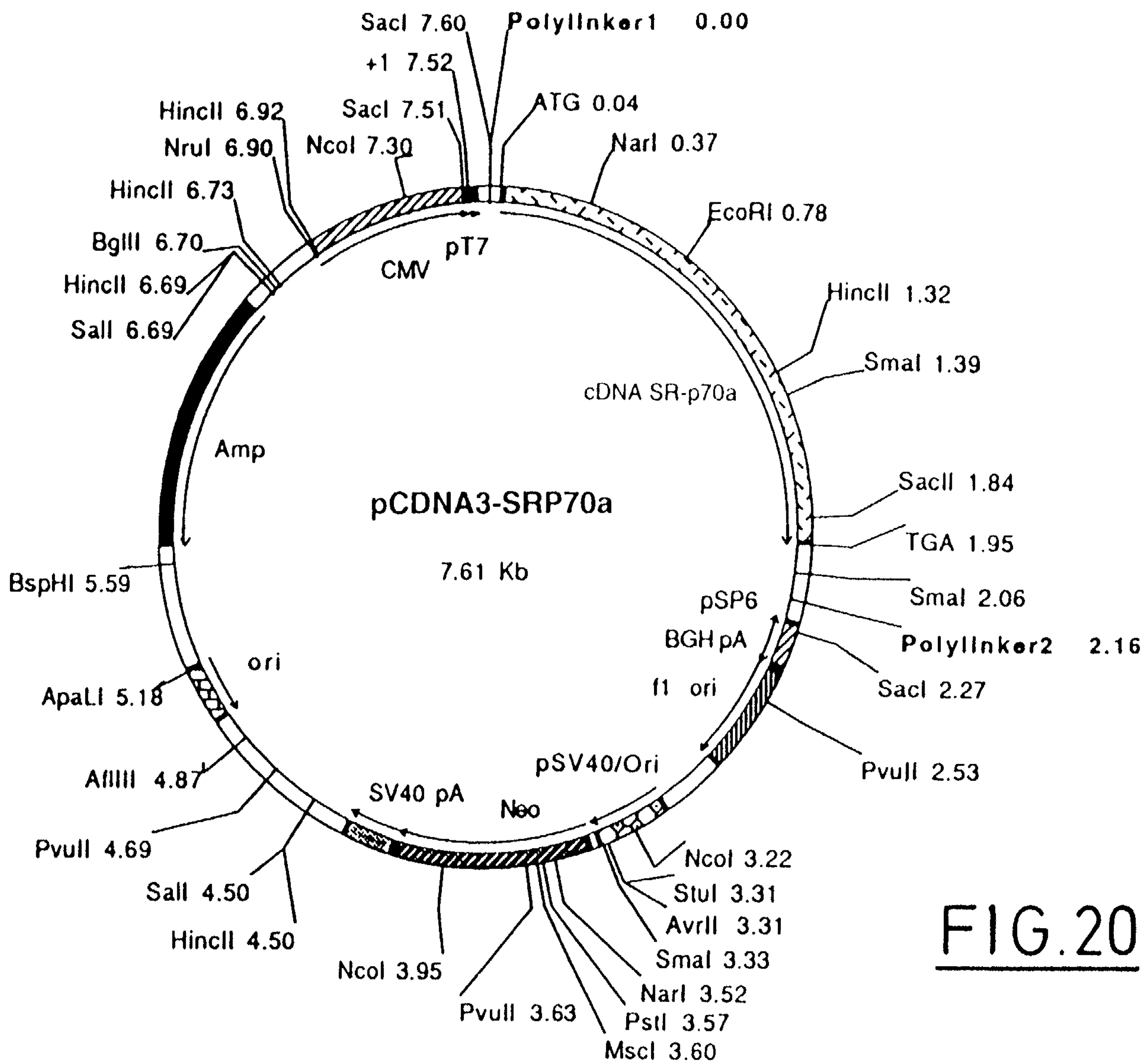


FIG.20

Polylinker1: 0.0/HindIII.NotI.KpnI.
Polylinker2: 2.16/XbaI.NotI.ApaI.

DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

X Original ______ Supplemental ______ Substitute

As a below-named inventor, I hereby declare that:

My residence, citizenship and post office address are given below under my name.

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Purified SR-p70 protein

the specification of which

____ is attached hereto.

X was filed on ________________ as United States Application Serial No. ________________ and was amended on ________________ (if applicable).

____ was filed on February 03, 1997 as PCT International Application No. PCT/FR97/00214 and was amended under PCT Article 19 on September 02, 1997 (if applicable).

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge my duty to disclose information of which I am aware which is material to the examination of this application in accordance with Section 1.56 of Title 37 of the Code of Federal Regulations.

I hereby claim foreign priority benefit under Section 119 (a) - (d) of Title 35 of the United States Code of any foreign application(s) for patent or inventor's certificate or of any PCT application(s) designating at least one country other than the United States identified below and also identify below any foreign application(s) for patent or inventor's certificate or any PCT application(s) designating at least one country other than the United States filed by me on the same subject matter and having a filing date before that of the application(s) from which priority is claimed:

			Priority Claimed	
Country	Number	Filing Date	Yes	No
FRANCE	96 01309	February 02, 1996	X	

I hereby claim benefit under Section 120 of Title 35 of the United States Code of any United States application(s) or PCT application(s) designating the United States identified below and, insofar as the subject matter of each of the claims of this application is not disclosed in said prior application(s) in the manner provided by the first paragraph of Section 112 of Title 35 of the United States Code, I acknowledge my duty to disclose material information of which I am aware as defined in Section 1.56 of Title 37 of the Code of Federal Regulations which occurred between the filing date of the prior application(s) and the national or PCT filing date of this application:

Application Serial No.	Filing Date	Status

I hereby appoint Mary P. Bauman, Reg. No. 31,926; Michael D. Alexander, Reg. No. 36,080; and Paul E. Dupont, Reg. No. 27,438, or any of them my attorneys or agents with full power of substitution and revocation to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

SEND CORRESPONDENCE TO:

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DIRECT TELEPHONE CALLS TO:

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I hereby declare that all statements made herein and in the above-identified specification of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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